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TREATMENT OF ADVANCED MALIGNANT DISEASE
Frank E. Adair, M. D.

BACTERIAL ENDOCARDITIS IN THE ELDERLY
Eugene F. Traut, M. D., J. Bailey Carter, M. D. and Stanley H. Gumbiner, M. D.

MANIFESTATIONS OF CHRONIC FOCAL INFECTION
Myer Solis-Cohen, M. D.

FUNGUS DISEASE OF THE LUNGS
John B. Andosca, M. D. and John A. Foley, M. D.

CONVULSIVE DISORDERS IN ADULTS
Robert L. Meller, M. D. and Joseph A. Resch, M. D.

Diagnostic Clinic

CANCER OF THE URINARY BLADDER
Gilbert J. Thomas, M. D.

Scientific Exhibit

ORTHOSTATIC HYPOTENSION AND ORTHOSTATIC TACHYCARDIA
Anton S. Yuskis, M.D. and George C. Griffith, M.D.

General Practice Review

TREATMENT OF ROSACEA • MANAGEMENT OF CASES WITH MENINGEAL SIGNS • TREATMENT OF CONGESTIVE HEART FAILURE

INDEX TO VOLUME VI
COMPLETE TABLE OF CONTENTS ON PAGE 5

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IT IS with considerable pride that we announce the addition of Dr. Morris Fishbein to our editorial executive staff as Contributing Editor. In placing his personal prestige, experience and many talents at the service of the official journal of the Interstate Postgraduate Medical Association, he has made a conscious and deliberate selection among the many medical journals which have attempted to enlist his co-operation.

FOR more than a generation few names have become more familiar to the medical profession than that of Dr. Fishbein. No other man in the medical field has ever had so long, wide and successful an editorial experience. Drawing on a lifetime of familiarity with medical progress, Dr. Fishbein is unique in his qualifications for writing live, vigorous and interesting editorials for Postgraduate Medicine each month. Even those doctors who do not always agree with him are always anxious to read what he has to say– in that cogent, straight-from-the-shoulder style which is so uniquely his own.

One of his most popular and delightful writing features has been "Dr. Pepys' Diary"– the dryly humorous story of Dr. Fishbein's encounters with interesting people both in and outside the world of medicine. "Dr. Pepys' Diary" will become a regular monthly feature in Postgraduate Medicine beginning with the January issue.

Dr. Fishbein has long traveled the world over in the interest of medicine. He has just returned from Europe and, under the heading of "Medicine Abroad," he will write each month the fascinating story of his experiences, acquaintances and conclusions on the development of international medicine.

IT HAS been our aim to make each issue of Postgraduate Medicine both *interesting* and of *real value* to the general practitioners, internists, general surgeons and other specialists, first by including the type of material which would be found most useful and needful in their respective practices; secondly, by presenting such material and other editorial features in a highly colorful, and extremely readable manner. We believe that Dr. Fishbein's contributions will add even more vitality and readability to this distinguished journal.

A Preview of some of the Diagnostic Clinics to be Published During 1950

Management or Treatment of Neuroses in the General Hospital—by BALDWIN L. KEYES, Professor of Psychiatry, Jefferson Medical College, Philadelphia, Pa.

The Causes of Unsatisfactory Results after Operation on The Gall Bladder and Bile Ducts—by RICHARD B. CATTELL, Surgeon, Lahey Clinic, Boston, Mass.

The Management of Massive Gastrointestinal Hemorrhage—by J. WILLIAM HINTON, Professor of Clinical Surgery, Chairman, Department of Surgery, New York University-Bellevue Medical Center of New York University Post-Graduate Medical School, New York New York.

Laennec's Cirrhosis—by LEONARD G. ROWNTREE, Miami, Florida; Formerly Director of the Philadelphia Institute for Medical Research.

The Clinical Use of Histamine—by BAYARD T. HORTON, Head of Section in Division of Medicine, Mayo Clinic, Rochester, Minnesota.

Bilateral Laryngeal Paralysis—by CHEVALIER L. JACKSON, Professor and Head of the Department of Laryngology and Broncho-Esophagology, Temple University School of Medicine, Philadelphia, Pa.

Diseases of The Stomach and Duodenum—by WALTMAN WALTERS, Mayo Clinic, Rochester, Minn.

Pulmonary Suppuration—by EVARTS A. GRAHAM, Bixby Professor of Surgery and Head of the Department, Washington University School of Medicine, St. Louis, Missouri.

Management of Peptic Ulcer—by GEORGE CRILE, JR., Cleveland Clinic, Cleveland, Ohio.

The Differential Diagnosis of The Enlargements of The Kidney—by HERMAN L. KRETSCHMER, Professor of Urology (Surgery), University of Illinois College of Medicine, Chicago, Illinois.

Diverticulitis of The Colon by CHARLES W. MAYO, Surgical Section, Mayo Clinic, Rochester, Minnesota.

Ulcerative Colitis—by FRANK H. LAHEY, Director, Lahey Clinic, Boston, Massachusetts.

GENERAL PRACTICE *Review*

IN THIS unusual editorial department published every month, information is made available to the *general practitioner* on the latest proved methods of treatment of conditions *commonly* encountered in an average practice.

On the invitation of the Editors of POSTGRADUATE MEDICINE, leading specialists in all fields of medicine prepare brief, authoritative discussions of *preferred* and *proved* methods of the treatment of disease conditions doctors are most apt to encounter in their general practice.

GENERAL PRACTICE REVIEW will be found on page 480 of this issue.

Treatment of Advanced Malignant Disease

SYNTHETIC ESTROGENS AND X-RAY THERAPY

FRANK E. ADAIR*

CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK

Besides surgery, we have looked to x-ray and radium for our cures of cancer. Caustic paste has but a small place in cure, no matter how expertly applied, and the actual cautery has little place in the cure of cancer.

In cancer of the uterine cervix, the caustic effects of the gamma rays of radium directly applied to the cervix, backed up by high voltage x-ray therapy, have become the most common form of accepted therapy throughout the world. There is practically no operative mortality, and the percentage of cures when this form of therapy was initiated was definitely superior to the surgical therapy of uterine cancer. When John G. Clark of Philadelphia presented his famous paper comparing his cures by surgery in contrast to radium, the world swung from surgery, with its very high operative mortality of those days, to radium as the choice of therapy. Something, however, has recently happened. The still small voice of those who think and ask questions has become quite audible. Meigs of Boston has questioned the propriety of radiation in very early cases of cervical cancer; in these he operates. His operative mortality is only 1 per cent in this particular group.

Alexander Brunschwig has extended the surgical experiment to include all stages of uterine cancer. In order to compare five-year cures by surgery and radiation, he is treating every new case by surgery only. The generous use of whole blood, protein, calcium, penicillin, sulfa drugs, the oxygen tent, and the expert anesthetist has placed surgery of today in an entirely different sphere from that of ten years ago.

In my opinion, the trend of cures in cancer therapy is more and more in the direction of modern and daring surgery.

While the use of radium and x-rays belongs chiefly in the category of palliative rather than curative therapy, I am grateful to be able to obtain the benefits of such therapy. I have largely spent my professional life in an institution which has greatly emphasized radiation. I do not wish to hurt it or those great scientists who are even today extending its frontiers. However, as of this minute, if I personally had an operable cancer of the tongue, stomach, lung, breast, lip, skin, bone, colon, larynx, or rectum, I would select a good surgeon. That is my overall opinion of the efficiency of present day irradiation.

As any new form of therapy is coming onto the horizon, it is important that we comprehend its full significance, but be most cautious not to attach an overemphasis to its use. In the use of the synthetic androgens and estrogens, I wish to emphasize that these agents at present have their value not in cure but in palliation. I shall discuss their use only in breast cancer, and I reiterate that if the case is operable, I would depend for cure on radi-

*Associate Professor of Clinical Surgery, Cornell University Medical College; Attending Surgeon and Executive Officer, Medical Board, Memorial Hospital, New York, New York.

Presented November 10, 1948, before the meeting of the Interstate Postgraduate Medical Association of North America, Cleveland, Ohio.

cal mastectomy. I hope I will be forgiven if I attempt to emphasize a radical mastectomy and not that horrible procedure of a simple mastectomy backed up with x-ray therapy. Anyone can do a simple mastectomy, but it takes a surgeon to perform a radical mastectomy.

In the *operable* cases, by the radical operation, we obtain 84 per cent five-year survivals if the breast alone is involved, and 44 per cent if the breast and axilla are involved.

During the past years we have contributed very little to the five-year cure rate of those cases having the breast alone involved. Practically every good surgical clinic in the country should obtain approximately the same result. During the years past, however, we have doubled the number of five-year cures of those cases with axillary disease.

Bloodgood used to state that he had 21 per cent five-year cures for those operable cases having axillary involvement. Today, I think, largely due to the propaganda that the public should go to see the doctor early, people are still coming to us with 60 per cent involvement of the axillae *but* having much smaller numbers of axillary nodes involved and much smaller axillary masses. These are the factors which account for the doubling of our cure rate in those cases with operable axillary disease.

If one is able to give sufficient irradiation therapy to an involved area, the ideal result is calcification of the tissues and a locking up of the cancer cells within the scar tissue. This is the ideal that we hope to obtain by x-ray therapy.

X-ray therapy over a metastatic area can give a temporary holdback of the disease. Ordinarily, improvement does not last beyond a year or two when it involves bone. Here, a very dense area like callous is developed.

Recurrent disease on the chest wall is always very disturbing to the surgeon as it is difficult to cure. As a whole, we do not get cure often in these cases. We, therefore, must face the fact that we must depend upon x-ray and radium in such cases for palliation and not for cure.

CASTRATION

There is another approach to the problem of metastasis; namely, x-ray castration. By this method, palliation at times is nothing less than remarkable. We have cases where individual lesions were not treated by x-ray, but were treated only by castration by x-rays.

HORMONE THERAPY

I have taken 5,000 of our operable cases of breast cancer and divided them up by years. There are two main age groups where breast cancer develops in largest numbers. One is at the age of 45 years; the other is 60. The age of 45 is the time when changes are taking place leading to the menopause; something happens to the ovarian hormone output. The menstrual periods last fewer days and the flow becomes less in amount.

The age of 60 years—when cancer of the breast develops second in frequency—is the time when the ovarian hormone is lacking in older women.

THE importance of the hormones, androgens and estrogens, is not only that we are developing a new and valuable palliative therapy, but for the first time we have an agent which may eventually reveal the steps in the production of breast cancer; an agent which may some day show us at which level—the anterior hypophysis, the adrenal, or the ovary—the chain may be broken which produces a breast cancer.

Hormone therapy of advanced mammary cancer is a recent contribution to the subject. The general basic rule for consideration is to give the androgens to women who are under 60 years of age, and give the estrogens to those women who are over 60 years of age. This rule has been founded upon much clinical experience. If the young woman is given estrogens, the cancer is stimulated, the growth takes on a rapid course, and the patient is greatly harmed. This rule is the most important to keep in mind. It would seem from a study of the incidence curve of the age when mammary cancer most frequently develops, that the forty-fifth year is the commonest year for mammary cancer to develop. The average age of the menopause in New York City is 46½ years. This represents, therefore, that pre-menopausal period when either a change has taken place in the chemistry of the estrogens; or the period when the hypophysis is changing its stimulating rate; or the period when the adrenal inter-relationship with the ovaries is undergoing marked changes; or the sum total effect of these changes are producing an altered metabolism so that the duct lining of the breast is out from under the strict growth control of normal ovarian, adrenal, and hypophyseal function.

There are many fundamental physiologic activi-

ties of which we as yet know little. The endocrine field is slowly being revealed, and the probability is that during the ten years lying immediately ahead, discoveries of unexpected importance will be revealed in the hormone field. The fact that any chemical agent such as a synthetic steroid is capable of producing changes in a mass of cancer cells or the tissue immediately surrounding the cancer cells, is of fundamental importance.

The work of investigators, particularly in the past five years, has demonstrated that *larger* doses of the steroids are necessary if the tissue changes are to be effected. For example, when we used testosterone in daily doses of 10 mg., we only rarely were able to produce the reparative changes in bone tissue. However, when the dose was increased to 50 mg. per day, striking repair took place not only in the bones, but also in soft tissues such as lungs, liver, skin nodules, etc.

At the present time, the hormones in common usage, namely testosterone and stilbestrol, effect striking improvement in approximately 20 to 23 per cent of the cases. Obviously, this is not a high enough proportion to satisfy the physician. We naturally hope for a 100 per cent improvement. As we learn more of the exact dosage, of the exact timing of administration of the dose, etc., results should improve and furthermore, as new and improved hormones are produced, it is likely that there will be a corresponding improvement in results of therapy.

It is difficult to understand why a crystalline substance such as testosterone in oil should give better results when injected daily rather than every other day; however, it seems to be more effective when so given.

There are many cases of widespread bony metastases involving the skull, ribs, spine, pelvis, and femora in which it is almost impossible to give x-ray therapy over all involved areas. In this type of case, the hormones do their most brilliant work. Although 4 out of 5 cases are not improved at present with our therapeutic methods now employed, still a case where it has been successfully applied is most dramatic. In the case of bone, the metastatic lesion will heal with a restoration of the destroyed area, with the deposit of a dense area that simulates callous, with complete loss of pain, and with restoration of function. Together with these improvements, there also is that feeling of "well being" which is a part of the entire picture.

The blood picture is greatly improved under testosterone therapy. These cachectic patients are usually lacking in not only hemoglobin, but also in the total number of red blood cells. Seventeen of 70 cases treated by testosterone showed an increase in hemoglobin of at least 26 per cent; and in some of the cases, there was 100 per cent increase. Ten patients showed a rise of levels between 16 and 20 gm. There is increased bone marrow activity and an increase in the erythro-myelo ratio. The dose level of the cases having this striking improvement in the blood picture ranged between 200 and 300 mg. per week.

A common mistake is to discontinue therapy before the patient has shown any benefit. Many patients do not respond for at least two to three months, while some patients under daily doses will show improvement in three weeks. In one case of wide bone involvement, under testosterone propionate therapy given 50 mg. daily, the x-ray films demonstrated that the bone repair had taken place within thirty days from the inception of the injections. It is possible to give testosterone to advanced patients with breast cancer at any age without harm. It is my impression that bone metastasis responds to such androgen therapy more quickly than estrogen therapy.

THERE are only two things to be kept in mind about androgen therapy. There is a condition of high blood calcium where androgen therapy seems to make the patient violently ill if prolonged. The patient appears to go into shock. This was first brought out by Farrow and Woodard. It is probably due to damaged kidneys with inability to eliminate the excess calcium; the latter in some cases going up from the normal of 8 to 10 mg. to as high as 18 mg. The other symptom for which we clinicians must look is that of nitrogen retention resulting in edema of the ankles and cardiac insufficiency.

When giving estrogen therapy such as estinyl or diethylstilbestrol, some patients are made sick and nauseated, and we find it difficult to continue therapy. The dose now given for the former is 0.1 mg. t.i.d., and for the latter, 5 mg. t.i.d., after meals. Estrogen therapy, as we have previously shown, must be used only on women 60 years of age or older. Not infrequently bleeding from the uterus will occur; this is due to the fact that the effect of the estinyl or diethylstilbestrol therapy is to produce a hypertrophy of the uterine lining which

SIDE EFFECTS

	ANDROGENS, PER CENT	ESTROGENS, PER CENT
Hirsutism	34	0
Voice changes	33	0
Edema, lower extremities	30	37
Vaginal bleeding	0	17
Nausea	0	26

OBJECTIVE IMPROVEMENT

	ANDROGENS, PER CENT	ESTROGENS, PER CENT
Soft Tissues	15	23
Skin	15	19
Pleura	13	12
Liver	25	0
Lungs	8	0
Bones		
All bones	19	0
Cervical vertebrae	33	0
Lumbar vertebrae	11	0
Pelvis	24.5	0
Ribs	17	0

may be quite marked, resulting in copious bleeding. In one striking case of therapy in a 72-year-old lady, who had a large ulcerating cancer of the left breast, a complete healing (epithelization) took place within a period of five weeks, while under stilbestrol therapy.

The side effects of the androgens especially are at times very disturbing to women.

SUMMARY

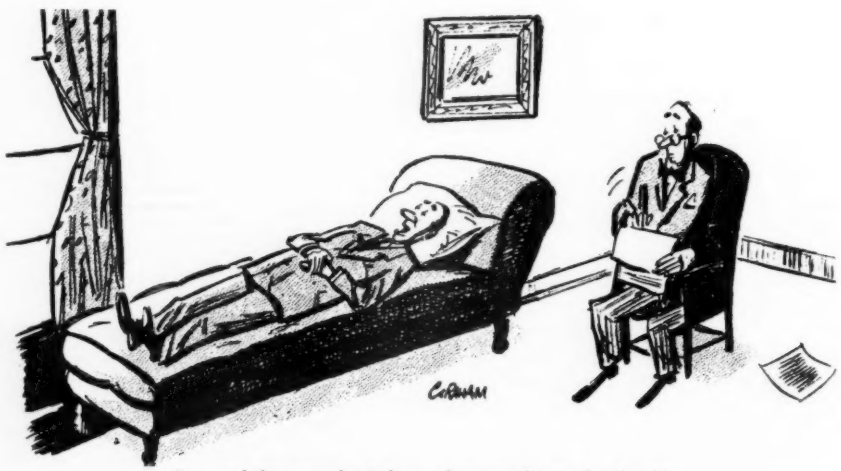
Surgery is the weapon upon which we must rely most for cure of mammary cancer.

X-ray therapy and hormone therapy are useful agents for palliation. It is too often true that we are disappointed in the results of both. Each, however, has its particular place. Many cases of advanced breast cancer are best palliated by x-ray therapy. Some cases with the disease so widespread as to make it impractical to employ the x-rays successfully, are better and more effectively treated by the hormones.

Estrogens are used only in the age group of 60 years or older.

Androgens can be used preferably in the younger age group. Testosterone therapy will cause temporary castration in the young.

A new field has been opened up in hormone therapy which encourages further exploration.



"... and then one day I dropped my mother on her head."

(Reproduced by permission of the proprietors of PUNCH.)

Bacterial Endocarditis in the Elderly

EUGENE F. TRAUT[1], J. BAILEY CARTER[2], and STANLEY H. GUMBINER[3]

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ACKNOWLEDGE of senescence and the care of the elderly is a function of the internist. Geriatrics[1] "should in no way obligate us to segregate a new medical specialty."[2] Aging processes are considered essential properties of all living matter.[3] Death from old age never occurs; it is always due to some disease. How age alters the reaction of the individual to disease becomes more important with the increasing number of older people in our population.

With advancing age inflammatory causes of death decrease; degenerative diseases and neoplasms increase. This age variation is most marked in cardiovascular disease. Rheumatic carditis is seldom seen in the elderly. Arteriosclerotic heart disease is rare in youth. Subacute bacterial endocarditis rarely, if ever, develops in a normal heart, antecedent cardiovascular abnormalities being anticipated in bacterial endocarditis regardless of the infecting agent.[4] Rheumatism, arteriosclerosis, syphilis,[5,6] or rarely a congenital defect[7,8] can provide a suitable basis for the endocardial localization of bacteria.*

Previous rheumatic endocarditis is the chief predisposing factor in bacterial endocarditis. Middleton[11] found rheumatic scars in 81.6 per cent of 88 cases and Christian[12] 89 per cent in 150 patients; the reported incidence varies from 65 to 90 per cent. These endocardial deformities may predispose to bacterial implantation in various ways. An altered tissue resistance or a predilection of scar tissue to reinfection can be the basis of the relationship of rheumatic fever and bacterial endocarditis.[13] Hemodynamics, altered by congenital defects or by acquired lesions resulting from inflammatory, toxic, or degenerative process, can explain the development of bacterial endocarditis.[14] Whatever the initial mechanism, the fundamental cause is local tissue anoxia.[15] Localization of the bacteria is determined mechanically. The organisms settle and multiply wherever they are sprayed forcibly on a receptive area.[16] Endocardial abnormality introduces the factor of increased intracardiac strain with resultant trauma.[13]

Because of its association with rheumatic carditis, subacute bacterial endocarditis has been considered an affliction of youth. But even in the elderly, rheumatic scars constitute the most common predisposing factor. Contrary to expectation, arteriosclerotic endocardial change is a much less common cause in the elderly. Syphilis is a factor.[6] Concomitant cardiovascular lesions of syphilis and bacterial endocarditis should be thoroughly examined for stigmata of rheumatic fever. Congenital defects are of much less importance in the elderly.

The importance of endocarditis in the elderly has only been recently recognized. In 1940 Willius[17] stated that "in the vast majority of cases the patients are less than 50 years of age." As a result of the more efficient medical and surgical means of preventing and curing bacterial endocarditis, more patients are living to develop recurrences or heart failure.

Protean manifestations characterize bacterial endocarditis generally. The clinical picture is particularly vague in the elderly. The symptoms are distinctly not cardiac.

Denman,[18] in 50 necropsied cases of subacute

*Koletsky[9] agrees with Gross[10] that a bicuspid aortic valve is not congenital but acquired, is nearly always of rheumatic origin, and this explains its frequent association with superimposed subacute bacterial endocarditis.

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EUGENE F. TRAUT

J. BAILEY CARTER

STANLEY H. GUMBINER

bacterial endocarditis, found dyspnea, pain, fever, weakness, chills, vomiting, paralysis, anemia, cough, loss of appetite, weight loss, nausea, palpitation, tarry stools, hematuria, hemoptysis, coma, nocturia, convulsions, epistaxis, night sweats, incontinence, jaundice, constipation or diarrhea, and nervousness, in this order. All had previous heart disease. Rheumatic scars were present in 23; 21 of the mitral and 10 of the aortic valve. Of 33 antemortem blood cultures 23 were positive and 10 were sterile. The Wassermann reaction was positive in 5 patients; none had necropsy findings of vascular syphilis.

Horder[19] states that indefinite symptoms and findings should lead to careful search for definite stigmata of endocardial infection.

Headache, irritability, insomnia, delirium, dizziness, mental confusion, stupor, and coma were some of the general symptoms.[20]

Of 165 cases,[21] clinical findings, by percentages, were: fever, 99.4; embolic phenomena, 57.7; petechiae, 54; pallor, 52.1; palpable spleen, 46.6; albuminuria, 45.3; oral sepsis, 42.3; hematuria, 40.7; clubbing of fingers, 37.4; Osler's nodes, 28.2; retinitis, 20.2; tooth extraction, 13.3; acute embolic onset, 6.7, and auricular fibrillation, 1.8. Erythrocytes were below 4,000,000 in 70 per cent. Leukocytes were below 10,000 in 56.5 per cent.

Subacute bacterial endocarditis should not be overlooked in the presence of normal leukocyte counts or leukopenia. Of the 58 cases coming to autopsy, the mitral valve was involved in 21, the aortic in 10, and the mitral and aortic in 14.

Gelfman,[22] in 115 cases of vegetative endocarditis studied pathologically, found that 74.8 per cent were below and 25.2 per cent above 50 years of age.

Of 28 autopsied cases[23] over 40 years of age, the antemortem diagnosis was correct in 14 cases. Positive blood cultures were present in all. Clinical findings of heart disease were present in 27 patients, changing murmurs being present in 12.

Zeman and Siegal[2] report 9 autopsied cases of acute ulcerative endocarditis over 60 years of age; none had been recognized clinically.

Zeman[24] reports 18 cases of subacute bacterial endocarditis, 14 with necropsy findings. Predisposing lesions were: rheumatic in 10; rheumatic and arteriosclerotic in 3; arteriosclerotic in 7; arteriosclerotic and syphilitic in 1, and congenital in 1 case.

DIAGNOSIS

Many cases of acute endocarditis in the elderly escape recognition because of difficulties in diagnosis. This is true of the febrile patients with bacteremia, but bacteremia may be present without active endocarditis. Sick old people are often hospitalized to await correct diagnosis at autopsy. There is a tendency to ascribe all complaints of the aged to arteriosclerosis. Low grade fever may be overlooked or ascribed to bronchopneumonia or urinary tract infection.

The site of origin of the endocardial infection is usually obscure. It may follow extraction of teeth

in predisposed individuals or surgical manipulation of other infected tissues. The occurrence of endocarditis following surgery of the genitourinary tract has not been sufficiently appreciated.*

Endocarditis is often overlooked in the elderly even in the presence of heart disease and symptoms, findings, or history of rheumatic infection. That heart failure in bacterial endocarditis has been clinically neglected is proved by necropsy findings. Inflammatory and degenerative changes occur in the heart muscle, often with infarction and abscess formation.

Electrocardiographic changes in subacute bacterial endocarditis may be few and insignificant. Conduction disturbances are less common in bacterial than in rheumatic endocarditis. In bacterial endocarditis a prolonged P-R interval occurs more commonly with aortic valvulitis than with mitral lesions.[25] Auricular fibrillation infrequently complicates bacterial endocarditis. It is apparently related to the functional integrity of the myocardium rather than to the degree of mitral stenosis.[25] The rarity of auricular fibrillation in subacute bacterial endocarditis is undependable as an aid in differential diagnosis.[26]

The cardiac manifestations of chronic valvular disease are more difficult to interpret in the elderly than in younger patients. A history of rheumatic fever is more often absent. Interpretation of auscultatory findings is more difficult. Cardiac murmurs may be absent, overlooked, or dismissed as arteriosclerotic, their cause and significance not being recognized. A systolic murmur may be due to rheumatic valvular disease, arteriosclerosis, or cardiac dilatation. With a murmur appearing suddenly, perforation of a valve cusp or rupture of a papillary muscle is to be considered. The quality of the murmur in subacute bacterial endocarditis may change from day to day. Difficulties in diagnosis, due to latency of the endocarditis, have been emphasized by Musser.[27]

The findings of meningitis, hemiplegia, or epilepsy, due to an embolic meningo-encephalitis, may produce the presenting and/or chief clinical feature of the disease.[20]

Such difficulties demand careful study. Four features characterize subacute bacterial endocarditis: "(a) a valvular defect or a congenital lesion, (b) fever, (c) emboli, and (d) a positive blood culture."[16]

*Traut, E. F., and Miller, C. O.: Endocarditis following surgical procedures. Proc. Chicago Urological Society, Jan. 22, 1948, and *J. Urol.* 62:598, 1949

DIFFERENTIAL DIAGNOSIS

The incidence of bacterial endocarditis and "the multiplicity, chronicity and duplicity of the disease" in the elderly deserve emphasis. Heart findings with signs of infection suggest rheumatic heart disease. Failure of penicillin to control infection suggests rheumatic or other nonbacterial process.[28,29] Verrucous, vegetative, and ulcerative endocarditis may occur simultaneously in the same patient and even on the same valve. Subacute endocarditis is more frequent than the acute bacterial process.

Many diseases simulate endocarditis. Hematuria, especially with azotemia, suggests renal disease. Symptoms and findings of thyrotoxicosis may confuse. A patient with thyroid dysfunction may develop bacterial endocarditis. Symptoms and findings of a "pleurisy," due to infarction of the dome of the spleen, may go unrecognized.[18] A "sterile meningitis" in an obscure febrile illness should suggest the possibility of a viridans endocarditis.[20]

In bacterial endocarditis involving the right side of the heart,[8,13,30] the clinical picture is predominantly one of pulmonary involvement. The lungs are an efficient filter and peripheral embolism and a positive blood culture are often absent until breakdown of a pulmonary infarct releases organisms into the systemic circulation.[7,21,31] Of 26,007 necropsies[32] there were 646 (2.5 per cent) with acute bacterial endocarditis; lesions were limited to the tricuspid valve in 20 cases. In only 8 of the 20 patients was a murmur heard and in no case was the murmur over the tricuspid area.

Conditions[33] most commonly confused with bacterial endocarditis are: grippe, rheumatic fever, renal calculus, meningococcus meningitis, pleurisy, tuberculosis, pneumonia, subarachnoid hemorrhage, brain tumor, brain abscess, cerebral hemorrhage, central nervous system syphilis, latent syphilis, and angina pectoris.

Endocarditis is less commonly mistaken[33] for: acute appendicitis, gallbladder colic, perforated peptic ulcer, coronary thrombosis, tuberculous meningitis, lumbago, neurosis, miliary tuberculosis, encephalitis, poliomyelitis, bronchitis, bronchiectasis, lung abscess, sinusitis, undulant fever, typhoid fever, typhus fever, pregnancy, perinephric abscess,

subphrenic abscess, pyelonephritis, hyperemesis gravidarum, idiopathic peritonitis, sarcoidosis, echinococcus cyst, and portal thrombophlebitis.

BLOOD CULTURES

Since organisms from the vegetations may only intermittently enter the blood stream, negative blood cultures make repeated attempts imperative. Cultures are made preferably at the peak of the fever, using at least 20 cc. of blood and seeding portions of the clot, with inhibiting antibodies removed by the serum, into a variety of highly nutrient media under varying oxygen tensions;[34] the proportion of positive cultures are directly dependent on the available bacteriologic skill.

MATERIALS

SINCE the literature at this time revealed only isolated instances of subacute bacterial endocarditis in the elderly, a review was made of pathologically proved cases of bacterial endocarditis in older patients.

Of a total of 13,661 autopsies at the Cook County Hospital (1935-1946) there were 299 cases of active endocarditis. Of these 299 cases 221 were of the bacterial or vegetative type. Of these 221 cases, 94 were over and 127 under 45 years of age. Two patients over 45 years of age died of verrucous endocarditis, uncomplicated by bacterial endocarditis. Such an occurrence is extremely rare. In the 94 cases pathologic findings were complete. These findings have been reported elsewhere.* In 12 of the 94 instances clinical records were not available; in 27 they were incomplete. There remained 55 cases in which clinical and necropsy findings were complete. The clinical findings of these 55 cases form the basis for this report.

Of the 55 cases there was cough in 13, heart pain in 6, and epigastric pain in 4 patients. Four patients gave a history of rheumatic fever. An enlarged heart was found in 25, systolic murmurs in 33, and diastolic murmurs in 21 patients. Heart failure was present in 41, edema in 10, and auricular fibrillation in 7 cases. Extrasystoles occurred in 3 and first degree heart block in 2 cases. The liver was felt in 21 and the spleen in only 1 patient. This agrees with the impression of Denman[18] that an enlarged and/or tender liver is a more characteristic early finding of acute endocarditis in the elderly than in splenomegaly.

The low incidence of palpable spleen, paralysis, petechiae, and the absence of Osler's nodes and clubbing of fingers have been noted.[21] Of 38 blood counts, 18 showed leukocytosis. In patients with subacute bacterial endocarditis leukocytosis is as frequently absent as it is present. The percentage of hemoglobin was below 75 per cent in 35 and below 60 per cent in 21 of the 38 patients. Microscopic hematuria was present in 7 instances. Antemortem blood cultures were made in 13 cases. Streptococcus viridans was found in 2; streptococcus hemolyticus in 3, and pneumococcus in 3 instances. Active endocarditis was correctly diagnosed as judged by autopsy in 12 cases. Other diagnoses were: salpingitis, urinary tract infection, encephalitis, meningitis, hemiplegia, and terminal.

An isolated instance which occurred near the completion of this study is here reported:

*Case 1**—A 57-year-old white male physician entered a hospital on April 14, 1946, with fatigue, fever, and weight loss for three weeks. These symptoms were noted one week after the extraction of 6 teeth.

Left heart enlargement, soft systolic aortic murmur, and a slightly tender liver edge 2 cm. below costal margin were found. Electrocardiogram was normal.

Ten blood cultures, aerobic and anaerobic, were negative. Hemoglobin 70 per cent, erythrocytes 3.5 million, leukocytes 6,000. Sedimentation rates varied from 47 to 118. Smears were negative for malaria. Urine revealed trace of albumin, chemical blood, and rare red blood cells.

Cholangitis secondary to an infected gallbladder was considered responsible for this obscure fever.

He was given 12,400,000 units of penicillin intramuscularly over thirty days. He left the hospital, against advice, on May 28, 1946, "feeling perfectly well" but with an afternoon temperature of 99.6° F. He gained weight, worked, and "felt well" except for 3 or 4 febrile bouts, the last to 105° F. with chills, just prior to readmission on August 25, 1947.

In addition to previous findings he had developed dyspnea and cyanosis, marked left heart enlargement with systolic-diastolic aortic murmur and râles in both lung bases. Clubbing of the fingers had developed. Blood cultures on August 26 showed indifferent streptococci. The organism was found sensitive to penicillin.

*This case history is presented to emphasize the fact that, in spite of pertinent knowledge accumulated over the six-year period during which "materials" were analyzed, this patient's illness, after comprehensive study and consultation, was not recognized until fifteen months later. The diagnosis of bacterial endocarditis in the elderly is still often difficult. If competent analysis of such a clinical enigma fails to establish a diagnosis, *adequate* penicillin therapy should be given to eliminate a possible bacterial endocarditis just as it should be given to a patient known to have the disease.

*Read in part at the Regional Meeting of the American College of Physicians, Milwaukee, 1947, and before the Chicago Pathological Society on December 13, 1948; the latter was published in the Transactions of the Chicago Pathological Society for 1948.

He received 1,000,000 units of penicillin intravenously daily.

At necropsy on September 2, 1947, ulcerative endocarditis was found engrafted on a stenotic, calcified, bicuspid aortic valve.

SUMMARY

1.67 per cent of 13,661 autopsies showed active endocarditis.

73.91 per cent of these patients had bacterial endocarditis.

42.53 per cent of the autopsies revealed bacterial endocarditis in people over 45 years of age.

The symptoms did not particularly point to heart disease.

Enlarged liver was common; splenomegaly uncommon.

Less than one-half of the patients had leukocytosis.

CONCLUSIONS

Infection plays an important role in heart disease of later life. Bacterial endocarditis is not unusual in patients over 45 years of age. Its frequency is underestimated.

As in youth, rheumatic valvulitis is the chief predisposing factor. Arteriosclerosis and syphilis play a more important role than in younger patients. Congenital lesions are less frequent.

Surgical manipulation of infected tissue, i.e., pulpless teeth, prostate gland, or cervix uteri achieve increasing importance as inciting causes in older patients.

Symptoms and even findings are vague, systemic, and not distinctly cardiac. Endocarditis should be considered and the blood should be cultured in patients with a heart murmur and fever, regardless of age.

Acute endocarditis in the elderly is frequently confused with the diseases more commonly seen in older patients.

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NERVOUS, FUNCTIONAL, AND ASTHENIC

Manifestations of Chronic Focal Infection

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Nervous, functional and asthenic symptoms frequently are toxic manifestations of chronic focal infection. When their focal infection origin is not recognized, patients presenting such symptoms may receive little or no benefit from the treatment given.

Unfortunately at the present time many physicians are skeptical as regards the etiologic role of focal infection. They have been shocked by the many unnecessary and harmful operations that have followed irrational conclusions that the coexistence of a disease and a focus of infection indicates that the focus is the cause of the disease.

Although the facts of focal infection have been recognized for hundreds and even thousands of years,[1] it is difficult and sometimes impossible to prove scientifically that a given morbid condition is caused by focal infection. The frequent failure to cure a disease associated with a focus of infection by removing infected tissue or evacuating pus at that focus has shaken confidence in the theory of focal infection. In the writer's opinion many of these failures are due to a common misconception as to what constitutes both focal infection and a focus of infection.[2]

FOCUS OF INFECTION

Most physicians have a mechanical or structural conception of a *focus of infection,* regarding it as a circumscribed area of infected tissue, such as a tonsil, an accessory nasal sinus, or an apical tooth abscess. The writer, on the contrary, adopts a bacterial conception and would define a focus of infection as infecting bacteria, pathogenic for their host and producing toxins inimical to him, which have their habitat in a more or less circumscribed area of tissue. When present in the throat, for instance, these infecting organisms are not confined to the tonsils, but as a rule are present also on the faucial pillars, in the nasopharynx, and on neighboring tissues. As tonsillectomy removes only those bacteria that are in the tonsils, it certainly does not remove the focus of infection in the throat, but merely substitutes tonsillar fossae for tonsillar tissue as a habitat for the bacteria. The bacterial focus of infection remains. Similarly, opening and draining a sinus undoubtedly get rid of large numbers of bacteria, but those that are left continue to multiply and to manufacture toxins and thus keep up the focus of infection.

FOCAL INFECTION

Focal infection[1] is not synonymous with a focus of infection. The infecting bacteria in a primary focus of infection often confine their activity to the tissues they inhabit, especially when the patient's bodily resistance is high. Lowering of the general resistance, however, enables these organisms or their toxins to be carried by the lymphatics or the blood stream to other more or less distant tissues,

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where the bacteria may form metastases or secondary foci of infection. At the same time their soluble exotoxins produce a bacterial systemic intoxication or toxemia with a host of general and local manifestations. It is this condition that constitutes focal infection.

It therefore is not surprising that mere removal of infected tissue frequently fails to cure a focal infection. In point of fact, focal infection and bacterial foci of infection are really removed only when the patient develops sufficient antibodies to destroy the infecting bacteria and neutralize their soluble toxins.

In every case of focal infection, whether or not any pathologic structural changes have been produced, the soluble exotoxins of the infecting bacteria cause a *bacterial toxemia* or *systemic intoxication*.[3] This is quite different from the toxic poisoning that occurs in diphtheria and tetanus in that it alters function rather than structure, its effect being chiefly symptomatic. The symptoms produced have no relation to the site of the focus of infection, being the same no matter where the latter is located. Nor are any of these symptoms peculiar to focal infection or pathognomonic of this condition, but occur also in other diseases.

These toxic symptoms are many and varied and may be separated into groups, according to their nature.

TOXIC SYMPTOMS

General and asthenic—Those symptoms which may be classed as general and asthenic are by far the most common. They include all degrees of physical fatigue—lassitude, lack of energy, fatigability, drowsiness, weakness, and exhaustion. Mental fatigue is shown by apathy, lack of mental vigor, loss of memory, difficulty in concentrating, slight mental confusion or "wooziness," difficulty in expressing oneself, inability to find the proper words, and disinclination to mental effort, such as making a decision. Other symptoms are headache, insomnia, a tendency to dream and to have nightmares, diminished sexual desire and power, malaise, anorexia, malnutrition, loss of weight or failure to gain, vertigo, faintness or actual fainting or semiconsciousness, slight rise in temperature, and, in children, acidosis. Pains, aches and stiffness make one suspect rheumatism.

Cardiac—Heart disease is suggested by dyspnea, palpitation, tachycardia, arrhythmia, weakness, fainting, precordial pains, and substernal pressure.

Nervous—Nervousness, irritability and depression are commonly present and, when combined with the asthenic symptoms, give the picture of nervous fatigue, nervous exhaustion, or neurasthenia. The patient usually attributes his depression to grief or business worries, which in many instances are borne without such depression in the absence of focal infection or other illness. Sometimes the depression deepens into melancholia, occasionally with suicidal tendencies. Other rare psychic phenomena are phobias, hypochrondriasis, hysteria, and psychasthenia. Paresthesias, diminished muscular power, twitchings or tics may also be observed.

Ocular—Eye symptoms met with are scotomata, temporary contractions of the field of vision, blurred or impaired vision of varying duration, probably due to fatigue of the muscles of accommodation, amblyopia and amaurosis for brief or longer periods, and tics or quivering of the eyelids.

Digestive tract—Frequently the toxic symptoms of focal infection affect the digestive tract[4] and appear as nervous indigestion, gastric neurosis, hyperacidity, anacidity, cardiospasm, pylorospasm, eructation, flatus, distention or bloating, intestinal spasms, accompanied by colicky pains and so-called "gas pains," irritable, spastic, unstable or "unhappy" colon, chronic colonospasm, atony of the colon, nervous or emotional diarrhea, mucous colitis, and intercostal or segmental neuralgia, simulating cholecystitis and appendicitis.

Allergic—In allergic individuals the bacterial toxemia commonly occurs as a bacterial allergy, with migraine, asthma, and urticaria or other dermatoses. Patients suffering from bacterial allergy frequently are thereby made more sensitive to other allergens, such as pollens, dander, shellfish, etc., which produce disturbances that disappear when the bacterial focus of infection is removed.

When the symptoms seem to point to disease of a certain system, the patient often consults or is referred to a physician specializing in diseases of that system, but who in many cases fails to recognize their focal infection origin or to discover or even look for the focus of infection.

One reason for the lack of attention to focal infection on the part of many skilled physicians is the absence of any scientific laboratory method of proving that a particular symptom is due to focal

infection. This is determined for the most part by careful clinical observation and analysis.

The attitude of the physician who is both a good clinician and a believer in scientific accuracy has been expressed by Hench,[5] who, after reviewing the arguments for and against the microbic theory of chronic rheumatic diseases, writes that as a clinical investigator he must conclude that the cause of atrophic arthritis is still unknown and that the evidence for infection, although very impressive, is incomplete. As a practicing physician, however, he cannot wait until the evidence is complete but is forced by the exigencies of practice to express an opinion one way or another and therefore has committed himself, with reservations, to the microbic theory.

RECOGNITION OF FOCAL INFECTION

In recognizing the focal infection origin of these functional, nervous and asthenic manifestations, the medical history is of great importance. Careful questioning may elicit a story of frequent attacks of acute upper respiratory infection or of many exacerbations of a chronic infection of the upper air passages. The presence of a chronic nasal or postnasal discharge, especially with the expulsion of ethmoid clots, points to chronic sinusitis.

A chronic cough or chronic bronchitis or even bronchiectasis may be secondary to chronic infection of the nasal accessory sinuses. Accentuation of symptoms with recurrent "colds" also points to their origin in a chronic sinusitis. The fact that the patient has had his tonsils removed or has had operations on his nose or sinuses, in the writer's opinion suggests the presence of a chronic bacterial upper respiratory infection rather than eliminates it. Similarly, the extraction of abscessed teeth is no indication that the dental focus of infection has been removed, because frequently a piece of infected root is left behind. The latter is especially to be suspected when the symptoms have their onset shortly after such an extraction.

The simultaneous presence of a number of the toxic symptoms frequently found in focal infection leads one to suspect the existence of a focus of infection. In many instances a patient who has been treated by a number of competent physicians without benefit will be found to be suffering from an unrecognized focal infection, especially when after thorough examinations which have proved negative, he has been told there is nothing the matter with him.

While it is possible that the nervous symptoms described may have a truly neurogenic origin, it is equally possible that they are due to a bacterial toxemia. Similarly, symptoms simulating organic disease may be due to a toxic upset of the nervous control of the functions of the organs affected. Cardiac symptoms with a normal heart; gastrointestinal symptoms with a negative radiographic study of the stomach, intestines, and colon; urinary symptoms with negative cystoscopy, ureteroscopy, cholography, and urinary findings; eye symptoms in normal eyes—all suggest a bacterial intoxication due to focal infection.

A NEGATIVE report from a rhinolaryngologist merely means that no abnormality was observed.[6,7] The fact that no pus was seen in the nose, however, does not eliminate infection and thickening of the lining membrane of the sinuses, which the x-ray would disclose. Nor does evidence that the tonsils have been well removed mean that there is no bacterial focus of infection in the throat. A reddened fauces, with red streaks on the pillars, indicates the presence of infection there or in the sinuses. Embedded tonsils sometimes are not visualized until the faucial pillars are pulled aside or the tonsils are brought into view by pressure. When liquid pus is expressed from the tonsils there is no question as to their being infected, no matter how innocent they may look on ordinary inspection.

Spaces where teeth have been removed are frequently ignored by physician, dentist, and radiologist although, until they are radiographed, one cannot be sure that an infected root fragment is not present.

One of the things that make the writer strongly suspect a focal infection origin of symptoms is their failure to be relieved by the therapeutic measures that usually cure them.

A bacterial smear or an ordinary bacterial culture gives no information as to the existence of focal infection. They merely show the organisms, or some of them, that are present. They give no information as to whether any of these organisms are infecting the patient or even whether they are capable of infecting him. This information, which is related to his specific resistance or immunity to such organisms, is furnished by the *pathogen-*

selective culture, in which the organisms are planted in vitro in the patient's whole, coagulable blood.[8,9] Those organisms that are able to grow in his blood are believed to be capable of infecting him, while those that are killed by his blood are regarded as nonpathogenic for him. The ordinary culture, moreover, misses from 2.5 to 18 per cent of the infecting organisms that are picked up by the pathogen-selective method.[10]

Even the discovery of a focus of infection is not evidence that the patient is suffering from focal infection or that his symptoms are due to a toxemia originating in that focus. It is, however, justifiable to suspect the presence of a focal infection, when the same infecting organism is found in a number of foci, such as the nares, the tonsils and the nasopharynx, in an aural discharge and the urine, or in the upper respiratory tract and an apical abscess, especially if only one infecting organism is found in a number of foci.

Particularly suggestive clinical evidence is furnished by the exacerbation of symptoms following an excessive dose of a vaccine-filtrate made from pathogen-selective cultures of the focus or by their amelioration or disappearance following an appropriate dose, with their reappearance or exacerbation when the effect of this dose has worn off, and their subsequent amelioration or disappearance after another appropriate dose.

TREATMENT

Treatment of the toxic symptoms of focal infection should be the treatment of the focal infection. Symptomatic treatment as a rule gives no, or only temporary, relief. The chief indication is to discover and to treat the causal focus or the foci of infection.

Usually it is necessary to remove an abscessed tooth or diseased tonsils and to open and drain a cavity containing pus, although it must be borne in mind that, except in the case of the tooth, this of itself does not remove a focus of infection.[11] Moreover, one should appreciate the seriousness of such operations in the presence of focal infection. The trauma of the operation may further lower the patient's resistance to such an extent that the infecting bacteria remaining at the operative site take on renewed pathogenic activity and light up other foci which hitherto had been quiescent, often with fatal results. Shock may be minimized by extreme gentleness in the operative procedure and by giving a blood transfusion prior to it.

The bactericidal action of the patient's blood to the organisms circulating in it directly following the operation may be raised by the administration of penicillin or a sulfonamide for two days prior to and for two days subsequent to the operation, by transfusion with blood that is bactericidal to the infecting organism, by rest in bed following the operation, and by preoperative inoculations of a pathogen-selective vaccine-filtrate.

When the membrane lining the sinuses is infected and thickened, in the absence of pus, the x-ray can often reduce it without the serious consequences that so frequently follow its curettement. The radiologist necessarily must be one experienced in this treatment if the best results are to be obtained.

The next step is the removal of the bacterial focus of infection, which is likely to remain after the operation. Although penicillin and the sulfonamides are employed by many physicians for this purpose, they have not proved efficacious in the writer's hands nor does their use in chronic infections seem to him logical or proper, as these drugs should not be given indefinitely or for long periods of time, and their immediate beneficial action does not persist long after their administration has been stopped.

Disinfectants may reduce the number of bacteria but they never sterilize completely and, while valuable adjuvants, do not cure.

The principal indication, in the writer's opinion, is to increase the production of the patient's bactericidins—in order to destroy the infecting organisms, and of his antitoxin—in order to neutralize their soluble exotoxins. When his resistance is not very low it sometimes may be raised by general hygienic measures, supplemented perhaps by tonic therapy.

In the majority of the writer's cases, however, it has been necessary to stimulate antibody production artificially by means of a pathogen-selective vaccine-filtrate, which contains not only the infecting organisms with their endotoxins but also their soluble exotoxins, which are necessary to stimulate the manufacture of specific antitoxins in order to relieve the toxic manifestations.

Inasmuch as the pathogen-selective vaccine-filtrate is very potent and patients differ so very widely in their degrees of sensitivity to it, its ad-

ministration must be carefully individualized. One patient may require a dose a million or a billion times greater than that required by another.

The writer determines the first subcutaneous therapeutic dose from the local reactions to three simultaneous intracutaneous test doses, each ten to a thousand times larger than the other. Subsequent subcutaneous therapeutic doses are determined according to the general, focal, and local reactions produced by the previous dose.[12]

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(From "The Medical Pickwick")

Great Moments in the History of Medicine
Dr. Gaa Bhoi, a near-sighted Chinese physician, invents eye glasses, July 5, 3608 B.C.

Fungus Disease of the Lungs

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Fungus disease of the lungs presents no distinctive clinical picture and may simulate a number of well-known pulmonary conditions. A correct diagnosis at times can only be made after the most careful and exhaustive investigation.

The primary infection most often occurs through the respiratory tract. Sufficient damage to the mucosa permits the yeast to gain a foothold in the lung tissues bordering the bronchi. At some stage in the spread of the disease, either through ulcerations or caseations a large number of organisms gain entrance into the blood or lymph stream. These may be deposited all over the body especially in the lungs, brain, liver, kidneys, and bones. Probably the majority of yeast infections never get beyond the bronchi; a few reach the peribronchial tissues, the lung parenchyma, lymph nodes, and the pleura.

Microscopically the pure lesion of a mycotic infection is a tubercle-like granuloma. The central area is caseous, devoid of epithelioid cells, sometimes containing giant cells. Abscess formation is a common occurrence and many yeast spherules are often found in the contents of the abscesses.

The clinical symptoms of fungus disease vary in degree and type depending upon the virulence of the infection, extent of the disease, and rapidity of extension. In mild cases the symptoms are those associated with any pulmonary infection. The patient usually complains of a mild cough, occasional chest pain, and loss of strength. In severe cases there may be such symptoms as severe cough, expectoration, dyspnea, hemoptysis, and fever. The sputum may have a foul odor.

Physical examinations of the lungs often fail to reveal any abnormal finding, although in some cases the physical signs of dullness, râles, and cavitation may be obtained. The clinician is usually the first to encounter the condition. The radiologist's interpretation of the roentgenograms is of the greatest importance. The bacteriologist usually confirms the diagnosis by demonstrating the presence of the fungus itself.

It is interesting to note that the symptoms, physical examination, and roentgenograms may simulate any type of inflammatory process in the lung. At times the lesion may resemble tuberculosis, carcinoma, sarcoidosis, pneumonia, bronchiectasis, bronchopneumonia, Löffler's syndrome, and pneumoconiosis. It must be remembered that fungi are often found as secondary invaders in any of the above-mentioned pulmonary conditions. The clinician, the radiologist, and bacteriologist should always work as a team in arriving at a diagnosis.

Saturated potassium iodide by mouth and sodium iodide intravenously often give excellent results. Sulfonamide and penicillin therapy should always be tried in cases that do not respond to iodides. X-ray radiation given over the chest and skin lesions has also been employed.

MONILIASIS

Bronchopulmonary moniliasis has been described as an infection of the lungs caused by the Monilia albicans and characterized by a chronic and usually progressive course. For some time moniliasis was considered to be quite rare, but recently it has been found to be more prevalent than was generally suspected.

Monilia, which is widely distributed in nature, represents a genus comprising a number of species and possible varieties. It exists as a saprophyte, but is believed to become parasitic under certain conditions. This yeast-like fungus may be cultured

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satisfactorily on artificial media in aerobic and semi-aerobic conditions. The fungus produces white colonies on Sabouraud's medium resembling Staphylococcus albus. It reproduces by budding and the formation of mycelia.

Monilial infections of most of the organs of the body have been described. The diagnosis of bronchopulmonary moniliasis cannot be made on clinical or radiologic findings alone; the laboratory must be the final and deciding agent in arriving at a correct diagnosis. Again the mere presence of monilial fungi in the sputum does not confirm a diagnosis of moniliasis (Figure 1).

Costellani[1] postulated that the presence of monilias offered three possibilities: (1) the monilias were nonpathogenic and nonvirulent; (2) they were secondary invaders; (3) they were virulent and the true basis of the disease.

His criteria for the latter was the production of lesions in the lungs of animals inoculated with the isolated monilias. It has been noted radiologically that the process starts in the hilar regions of the lung and spreads outwards and basally. The apices are rarely affected primarily.

Three clinical forms of the disease have been described: a mild form characterized by bronchitic symptoms; an intermediate form with symptoms commonly seen in early stages of pulmonary tuberculosis; a severe form simulating ulcerative tuberculosis which is often fatal. The principal symptoms encountered are fatigue, loss of appetite and weight, streaked sputum or hemoptysis, cough, expectoration, chills, fever, night sweats, and dyspnea of varying degrees.

THE majority of cases respond fairly well to iodide therapy both orally and intravenously. Some workers have employed an autogenous vaccine of monilia with some success. Still others have employed sulfonamides, penicillin, and x-ray therapy with beneficial results. It is safe to say that if the disease has progressed too far before treatment is instituted, a fatal outcome is inevitable.

Case 1—F. F., a 19-year-old white, single, male grocery clerk was admitted to the Boston Sanatorium with a six months' history of weakness, dyspnea on exertion, cough, expectoration, loss of appetite and loss of 15 pounds in weight. Sputum tests for tubercle bacilli were persistently negative, including gastric aspiration and guinea pig inocu-

lation tests. The other laboratory data were essentially negative.

In view of the negative sputum, serial roentgenograms, and physical findings limited to the lower two-thirds of both lungs, fungus disease was suspected (Figure 2). Sputum cultivated on Sabouraud's medium revealed the presence of a pure culture of Monilia albicans.

Despite iodide therapy both by mouth and intravenously the patient died.

Autopsy report—Anatomic diagnosis: Bronchiectasis with multiple abscesses of right and left lower lobes. Bronchopneumonia of upper lobes. Microscopic diagnosis: Monilia albicans.

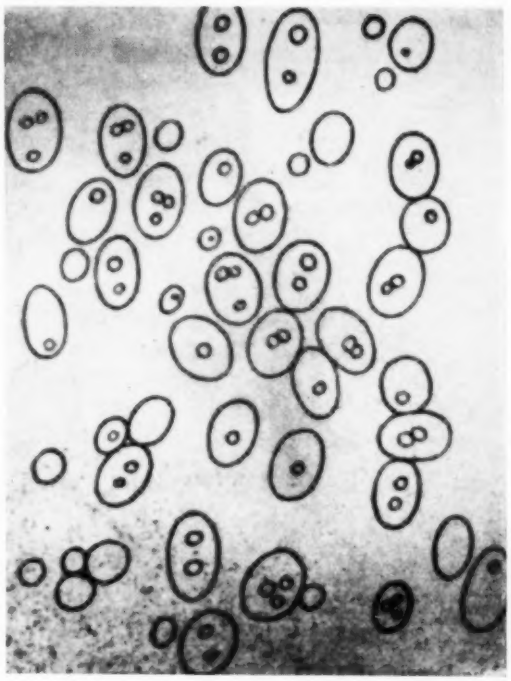

FIGURE 1. Monilia tropicalis of Castellani.

ACTINOMYCOSIS

Actinomycosis is rather an uncommon disease, yet it has been recognized for years. Israel[2] in 1878 described the first clinical picture of actinomycosis in man. Since that time much has been written on the subject and cases of actinomycosis occurring practically in every organ of the body have been reported.

The parts of the body affected in order of frequency are: the head and neck, infection taking place through the mouth and pharynx; the chest, being infected via the respiratory tract; the abdominal viscera, the source of the infection being the alimentary tract. Abscesses form commonly near the breast and axilla later resulting in the formation of sinuses. The ribs are invaded in 25 per cent of the cases, the vertebrae in 10 per cent.

It is interesting to note that nearly 80 per cent of the patients affected are males. The diagnosis is usually made during life by the finding of the typical sulfur granules in the sputum. When the sputum or pus containing the granules is diluted with a large volume of water, the granules tend to sink to the bottom. When the material is examined in the fresh state under the low power of the microscope, a sulfur granule has a relatively transparent central portion with a narrow margin which is irregular and much more opaque. When examined under high power, the characteristic club-shaped bodies or rays are seen (Figure 3).

Characteristically these fungi produce a chronic granulomatous type of inflammation in which suppuration, abscesses, and sinuses develop, and dense scar tissue is produced in excess. The inflammation burrows through tissue with little or no respect for normal fascial planes and anatomic barriers. Superimposed upon the actinomycotic process, there is often secondary infection due to pyogenic bacteria.

Clinical symptoms are initiated quite consistently with a cough, at first unproductive and then with mucoid sputum which later becomes purulent and often streaked with blood. Frank hemorrhage is rare. Fever, dyspnea, malaise, night sweats, loss of appetite and weight ensue. Pain develops when the pleura is involved. Most of the successful treatments have included massive doses of iodides, sulfonamide therapy, thymol, x-ray radiation, and surgical drainage. Poppe[3] has employed penicillin quite effectively in controlling the severe toxic symptoms present in extensive actinomycosis between stages of surgical drainage.

We should not lose sight of the fact that actinomycosis is a chronic disease with remissions and spreads. Consequently, patients should be observed for a number of years before being classified as cured.

Case 2—A. S., a 52-year-old white, married machine operator was admitted to the main hospital with discharging

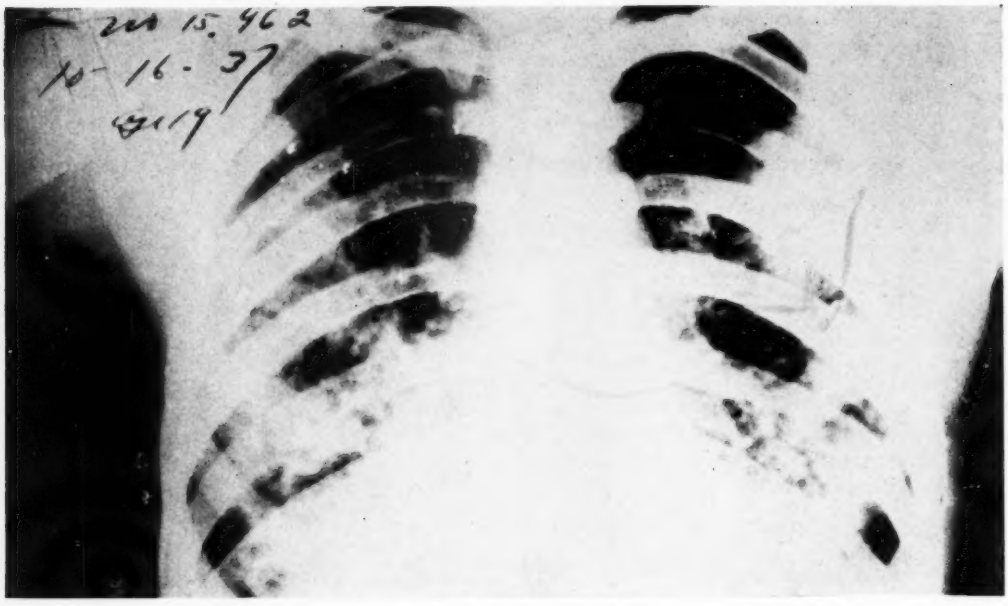

FIGURE 2 *(Case 1)*. Diffuse mottling with marked bronchopneumonic reaction involving the lower three-fourths of both lung fields.

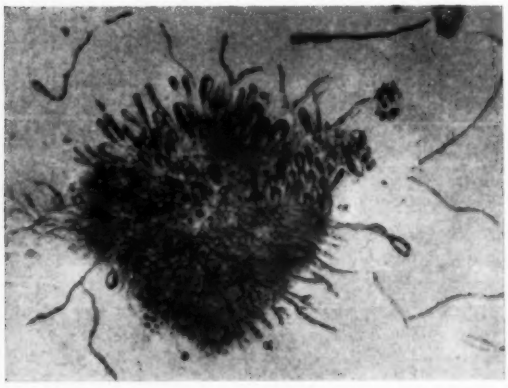

FIGURE 3. Actinomyces granula showing mycelium with club-shaped bodies.

sinuses and enlarged glands on the left side of the neck. In addition the patient complained of a morning nonproductive cough and generalized weakness.

A diagnosis of actinomycosis was made by the finding of the typical sulfur granules in the sputum and material obtained from the discharging neck sinuses. Sputum tests for tubercle bacilli were negative. Roentgenograms at this time revealed coarse infiltration in the region of the first left interspace (Figure 4). The patient was placed on sulfadiazine therapy, and 4 gm. daily was found to be sufficient to maintain a satisfactory blood level.

The patient made a complete recovery. The neck sinuses closed completely, and sputum examinations were repeatedly negative for actinomycosis.

One year later this patient was admitted to the Boston Sanatorium with a three months' history of cough, expectoration, occasional streaking, dyspnea on exertion, and loss of 15 pounds in weight.

In view of the previous history of actinomycosis, numerous sputum examinations for actinomycosis were made, but they were found to be negative. Examination of the sputum at this time was found to be positive for tubercle bacilli. Roentgenograms revealed coarse infiltration and cavitation in left upper lung field (Figure 5). Left artificial pneumothorax was attempted but was unsuccessful. A first stage (3 ribs) left-sided thoracoplasty was performed and the patient died on the twenty-first postoperative day.

Autopsy report—Tuberculosis of the left lung. Pneumonic consolidation of the right lung. Miliary tuberculosis of the spleen and liver.

It is interesting to note that the sulfadiazine therapy employed in this patient at the time of the actinomycotic infection was sufficient to bring about a complete cure of the disease, as no evidence of actinomycosis was detected at autopsy.

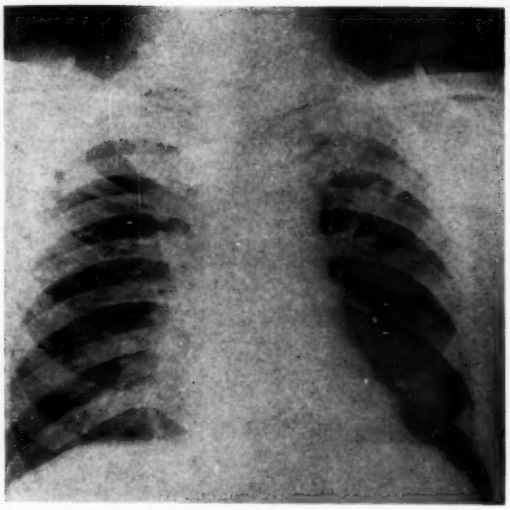

FIGURE 4 *(Case 2)*. Coarse infiltration with moderate bronchopneumonic reaction involving the upper one-third of the left lung field.

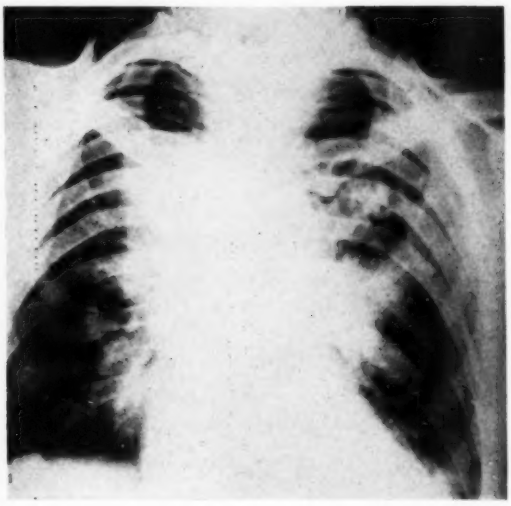

FIGURE 5 *(Case 2)*. Mottling with marked bronchopneumonic reaction involving the middle two-thirds of the left lung. Cavity in region of left hilus.

ASPERGILLOSIS

Relatively few species of aspergilli have manifested pathogenicity for human beings. Available data indicate that Aspergillus fumigatus has been isolated with greatest frequency from infections caused by the fungus, succeeded rather closely by Aspergillus niger.

Aspergillus glaucus, flavus, and nidulans are others implicated on occasion. The disease has been found most often in warm and damp climates. More males than females are affected. Most of the reported cases, both in man and in animals, have occurred in France.

The disease can only be recognized by the discovery of the mycelium or of the small rounded white or yellowish-white bodies in the sputum. Thom and Church[4] maintain that little difficulty need be anticipated in culturing and grossly classifying material from clinical sources, however, since the colony may be readily recognized as a component of this genus on the basis of its resemblance to a field of ripening grain, in which stalks and heads predominate (Figure 6).

The disease has been observed in persons who in some way handle grains, flour, or meal infected with the spores of the aspergillus. Certain species of birds, notably the pigeon, are excellent carriers of the disease.

Dieulafoy[5] and his co-workers in 1890 described several cases of pulmonary aspergillosis occurring in individuals engaged in the occupation of fattening pigeons.

Although the bronchopulmonary system is the most common site of infection, other parts of the body may be involved.

Bereston and Waring[6] recently reported a series of 13 cases of onychomycosis caused by the aspergillus. The nails of both hands and feet may be affected.

Rosenvold[7] reported a case of dacrocystitis in one patient and blepharitis in another as ophthalmic complications of aspergillus infection in the nose.

An abscess of the cerebrum caused by the aspergillus has been encountered, as has also fatal aspergillosis of the meninges.

THE signs, symptoms, and roentgenographic findings of pulmonary aspergillosis may simulate pulmonary tuberculosis very closely. There is considerable speculation as to when aspergillosis may be labeled primary or secondary. It is said

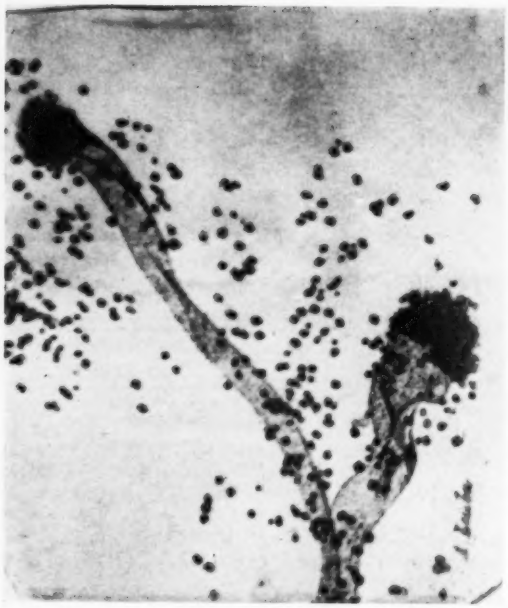

FIGURE 6. Aspergillus showing stalk with spore-bearing head.

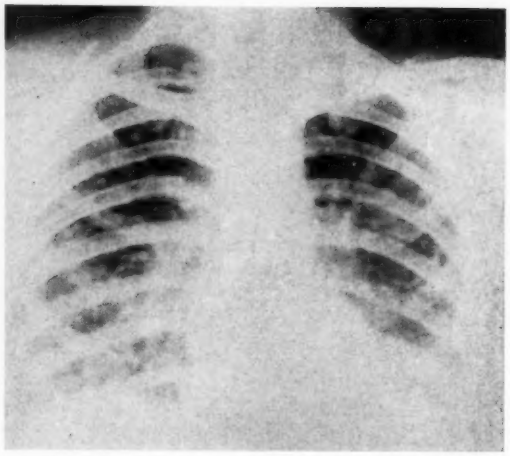

FIGURE 7 *(Case 3)*. Coarse infiltration and scattered nodulation involving both lung fields.

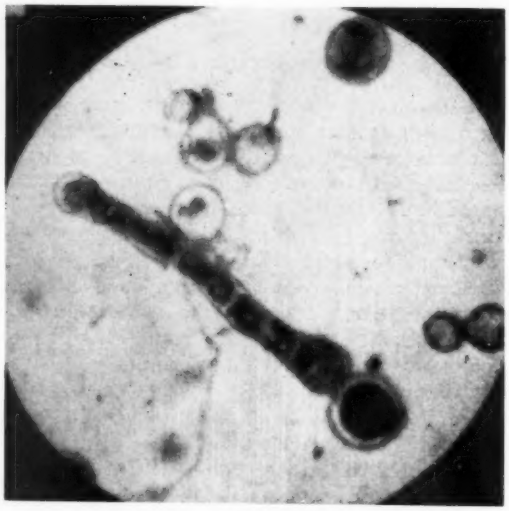

FIGURE 8. Blastomyces showing double contoured hyaline capsule, budding forms, and septate hyphae.

that carcinoma, tuberculosis, bronchiectasis, bronchial asthma, and allergic rhinitis have been cited as predisposing factors to this infection.

The term, primary aspergillosis, would be applicable to those cases in which the patient acquired the condition after prolonged exposure to massive doses of the organism. It appears that in a preponderance of recorded cases the disease has been of the secondary type.

The treatment of aspergillosis is often unsatisfactory. Intensive and prolonged administration of the iodides still remains the treatment of choice, but the prognosis in the majority of cases is poor.

Case 3—M. M., a 22-year-old white, single female was rejected for service in the W.A.C. because of x-ray findings at time of induction.

She was admitted to the Boston Sanatorium with a three months' history of slight cough, weakness, loss of appetite and 10 pounds in weight.

Sputum tests for tubercle bacilli were persistently negative, including gastric aspirations and guinea pig inoculation tests. The other laboratory data were essentially negative. In view of the negative sputum for tubercle bacilli, serial roentgenograms, and physical findings, fungus infection was suspected (Figure 7). Examination of the sputum revealed the presence of aspergilli. The patient was discharged as nontuberculous to the main hospital.

Despite intensive iodide and sulfonamide therapy, the patient died.

Autopsy report—Anatomic diagnosis: Multiple abscesses of right and left lower lobes. Bronchopneumonia of both upper lobes. Microscopic diagnosis: Aspergilli.

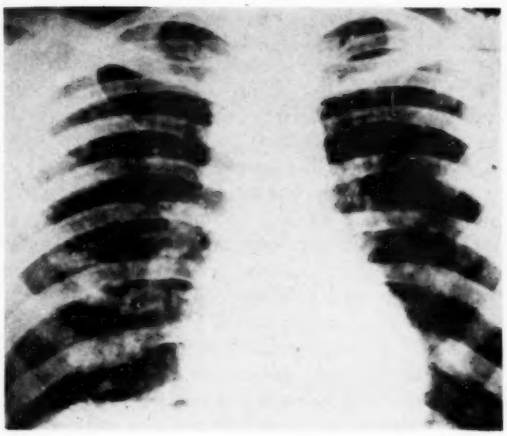

FIGURE 9 *(Case 4)*. Granular infiltration with moderate bronchopneumonic reaction involving the lower one-half of the right lung and left base.

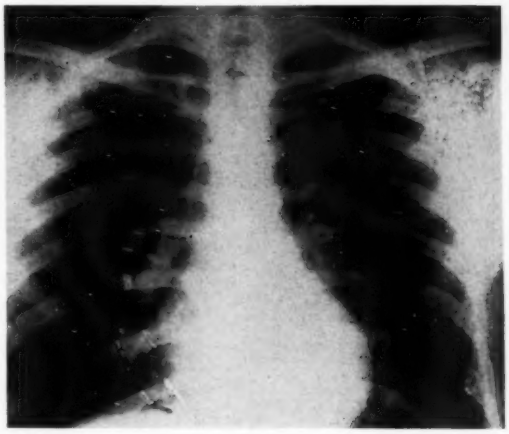

FIGURE 10 *(Case 4)*. Lung fields within normal limits.

BLASTOMYCOSIS

Since Gilchrist[8] in 1894 described the first case of blastomycosis in America, numerous investigators have made an intensive study of the condition. The organism causing this disease is a yeast-like fungus, spherical in shape and with a clear, double contour, 15 to 20 microns in diameter. The diagnosis is made usually by finding characteristic organisms in the sputum. Search for the organism is greatly facilitated by adding a 10 per cent solution of sodium hydroxide to the sputum. The specimen should be examined in the fresh state without staining (Figure 8).

In the great majority of cases in addition to the pulmonary involvement, there may be present blastomycotic lesions of the skin. These are characterized by elevated patches with a papillomatous surface and well-defined margins. The actual presence of the organism in the blood has been demonstrated. Among the other organs occasionally involved are the meninges, brain, kidneys, testes, and prostate.

In the systemic form of the disease, approximately 50 per cent will give a history referable to an upper respiratory infection. Symptoms and signs include those of a simple cold, such as cough, expectoration, streaking or hemoptysis, fever, chills, weakness, dyspnea, loss of appetite and weight.

The systemic cases are usually fatal, the patient dying with the clinical picture of tuberculosis. The mild cases usually respond to large doses of potassium iodide.

Desjardins[9] has employed x-ray therapy and diathermy in the treatment of this condition with fairly good results.

Martin and Smith[10] showed that good results could be obtained after the patient had been thoroughly desensitized by successive administration of subreaction doses of a dilute vaccine.

***Case 4*—J.** B., a 21-year-old white, single male was rejected for military service because of x-ray findings at the time of induction. He was admitted to the hospital with a six months' history of cough, slight expectoration of yellowish sputum, weakness, and loss of 10 pounds in weight.

Sputum examinations for tubercle bacilli were persistently negative including gastric aspiration and guinea pig inoculation tests.

Tuberculin skin tests were also found to be negative.

In view of the negative sputum for tubercle bacilli and roentgenograms, fungus disease of the lung was suspected (Figure 9).

Examinations of the sputum in the fresh state and with Sabouraud's medium revealed blastomyces.

The patient was placed on potassium iodide therapy. In two months the patient made a complete recovery as shown by the disappearance of symptoms and clearing in the roentgenograms (Figure 10).

COCCIDIOIDOMYCOSIS

Coccidioidomycosis was first reported in Argentina in 1892 by Posadas[11] and in America by Rixford[12] in 1894. Most of the cases of coccidioidomy-

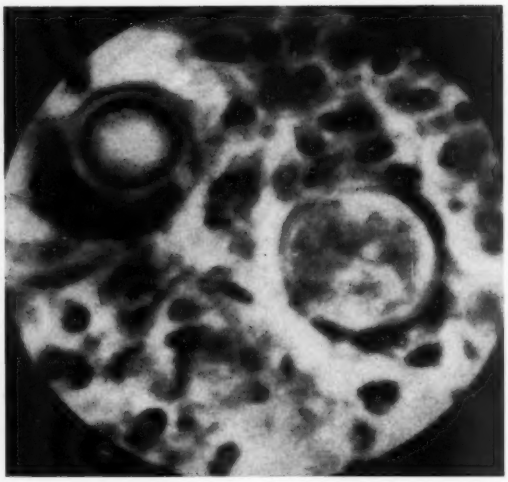

FIGURE 11. Coccidioides immitis showing double contoured hyaline capsule with typical endospores.

cosis infection in this country have been reported from California, Arizona, and New Mexico. The etiologic agent is the Coccidioides immitis. There are two known forms appearing in the life cycle, the vegetable form and the parasitic form.

The vegetable form presumably is found in nature and in culture. During the life history of this vegetable form, fungus hyphae are produced which in turn give rise to chlamydospores. These are probably disseminated by air currents and become deposited in the soil and surrounding plant life. Human or animal infection is then accomplished by the inspiration of spore-bearing dust. If sputum or tissue infected with the coccidioidal organism is examined microscopically, a spherical organism of 5 to 60 microns in diameter is seen, with a highly refractive double capsule (Figure 11).

In many instances this condition begins as a pulmonary infection and the picture simulates tuberculosis. There may be cough, hemoptysis, weakness, fever, loss of appetite and weight. Pleural effusion is not an uncommon finding. Organisms may be recovered from the pleural fluid. The roentgenographic findings of pulmonary involvement in these cases may vary considerably.

The most frequent lesion is a solitary nodose area of infiltration that later breaks down, leaving a thin-walled cavity. At times the nodose lesions are scattered throughout the lung so that they give the appearance of metastatic carcinoma. Other cases give an x-ray picture simulating pulmonary tuberculosis. A good majority of cases show slight enlargement of the hilar lymph nodes.

Aronson[13] and his co-workers made a study of a group of persons showing areas of lung fibrosis with associated calcified nodules which gave positive coccidioidin skin tests and negative tuberculin tests. They concluded that the parenchymal scars were due to coccidioidomycosis.

Goldstein and McDonald[14] in a review of 75 cases of primary pulmonary coccidioidomycosis were unable to find any calcification of the lesions. They maintained that the noncalcified hila in primary pulmonary coccidioidomycosis was a very important diagnostic feature in differentiating this condition from pulmonary tuberculosis.

There is no doubt that when pulmonary cavitation is seen by roentgenograms, the resemblance to tuberculosis is very striking. It is of the utmost importance to differentiate between the two conditions since the treatment and prognosis are very different. Coccidioidal cavitation is a benign process and the prognosis is quite favorable.

Recovery from the acute phase of this infection occurs commonly in several months. There may be dissemination of the organism to other parts of the body, resulting in a chronic progressive disease, with a fatality of 50 per cent.

All forms of therapy in the treatment of this condition appear to be unsatisfactory. No definite results have been noted from any drug therapy although Jacobson[15] has obtained encouraging results by means of colloidal copper and coccidioidin-B.

Treatment of patients with pulmonary cavities is still unsettled. These patients are apparently immune to dissemination and there is no evidence to show that the fungus spreads from cavities to adjacent pulmonary tissue.

Most cavities appear to heal spontaneously. Patients with such lesions are usually in good health and suffer no apparent ill effects, except occasional streaking and hemoptysis in a small number of cases. Denenholz and Cheney[16] have advocated the use of pneumothorax in such cases. There is no doubt that this procedure should be employed in patients with profuse hemoptysis. If pneumothorax is unsuccessful, phreniclasis should be performed.

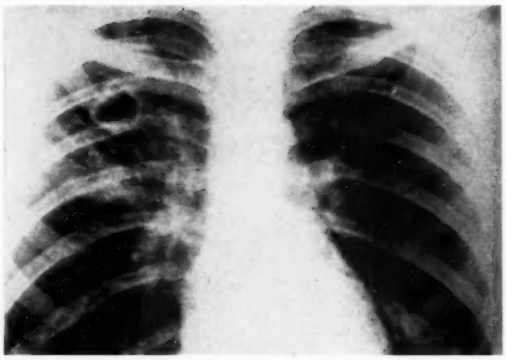

FIGURE 12 *(Case 5)*. Coarse infiltration with moderate bronchopneumonic reaction involving the right upper lobe. Cavity with fluid level in the right infraclavicular region.

FIGURE 13 *(Case 5)*. Infiltration with a thin-walled cavity in the right upper lung field. Exaggeration of the right hilar tree.

Case 5—P. R., a 21-year-old white male was accepted for military service and was stationed in the San Joaquin Valley, California, for eight months.

About six months later he developed a dry cough, some weakness, and loss of 15 pounds in weight.

Roentgenograms taken at this time revealed a cavity in the right upper lung field (Figure 12). Sputum examinations for tubercle bacilli were persistently negative, including gastric aspiration and guinea pig inoculation tests. Skin tests and cultures were found to be positive for Coccidioides immitis.

After eight months of hospitalization he was discharged from the Army.

Periodic roentgenograms still reveal the presence of a thin-walled cavity in the first right interspace (Figure 13). The patient is completely asymptomatic at the present time.

SUMMARY

1. A brief presentation with case records has been made of fungus infections of the lungs due to moniliasis, actinomycosis, aspergillosis, blastomycosis, and coccidioidomycosis.

2. Fungus diseases of the lungs are not common but when they do occur, the diagnosis should be made as early as possible before extensive damage occurs.

3. The clinical picture and roentgenograms may simulate tuberculosis, carcinoma, sarcoidosis, pneumonia, bronchiectasis, bronchopneumonia, Löffler's syndrome, and pneumoconiosis.

4. The clinician, radiologist, and bacteriologist should work as a team in making a correct diagnosis.

5. Most fungus infections of the lungs respond quite favorably to iodide, sulfonamide, penicillin, and vaccine therapy.

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Convulsive Disorders in Adults

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A CONVULSIVE disorder is a state produced by an abnormal, excessive neuronal discharge within the central nervous system. The clinical manifestations will be as diversified as the functions of the various cells of the nervous system. By the term convulsive disorder is meant epilepsy. It is felt that the new terminology is preferable for two reasons. First, the connotation of epilepsy to the average person is that of a horrible and incurable disease. Second, there is the danger of acceptance of epilepsy as the diagnosis of a disease entity in itself rather than consideration of it as a symptom of underlying pathology. To our way of thinking, a convulsive disorder implies that we are dealing with a symptom, the cause of which is also to be listed to complete the diagnosis.

The extent of this disability should be mentioned. About 650,000 people in the United States, roughly 1 in 200, have a convulsive disorder. However, figures cannot adequately express the plight of many of these people, especially the younger ones who, through the ostracism unwittingly imposed by the ignorance of the community, often lead lives of loneliness and frustration.

CLASSIFICATION OF THE CONVULSIVE DISORDERS

It was brought out in the definition of a convulsive disorder that the clinical manifestations would depend on the function of the group of cells which were over-reacting. For the sake of brevity the term "seizure" will be introduced at this time as being synonymous with convulsive disorder. The classification which is to be given is considered to be the most accurate since it gives a key to the location of the initial neuronal explosion in the pattern of the seizure to which the patient is subject. It is the clinico-anatomic classification of Penfield and Erickson.[1]

CLASSIFICATION OF CONVULSIVE DISORDERS

CLINICAL TYPE	LOCALIZATION
SOMATIC MOTOR SEIZURES	
Generalized seizure	Complete motor
Jacksonian seizure	Precentral gyrus, postcentral gyrus
Masticatory seizure	Postcentral gyrus
Simple adversive seizure	Frontal lobe
Tonic postural seizure (decerebrate); (opisthotonic)	Brain stem
SOMATIC SENSORY (AURAS)	
Somatosensory seizure	Prerolandic gyrus, postrolandic gyrus
Visual seizure	Occipital lobe
Auditory seizure	Temporal lobe
Vertiginous seizure	Temporal lobe
Olfactory seizure	Uncinate lobe
VISCERAL	
Autonomic seizures	Diencephalic
PSYCHICAL	
Dreamy state	Temporal lobe
Forced thinking	Frontal lobe
Stereotyped behavior	Frontal lobe
Automatism	
Petit mal	
Post-status epilepticus psychotic states	

The main feature of each of these seizures can be outlined as follows:

Somatic motor seizures—The *generalized seizure* or convulsion may be the end stage of any one of the other types. It is characterized by loss of consciousness, associated with tonic stiffening, and/or clonic jerks of the whole body, added to which there may be evidences of autonomic discharge such as micturition.

A *jacksonian seizure* consists of local movements of some part of the body; in a jacksonian "march"

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there is spread of the movement from one part of the body to another.

Masticatory seizures are attacks of smacking, salivation, chewing, and swallowing usually not remembered by the patient.

Simple adversive seizure involves a coordinated movement in which there is turning of the head, usually with a conjugate deviation of the eyes toward the side to which patient is turning. The movement continues until it produces a half turn or even several turns of the body before other phenomena supervene. It usually is associated with unconsciousness but need not be.

Tonic postural seizure results in rigidity of the trunk with extension of all extremities.

Somatic sensory seizures—*Somatosensory seizures* are transient or prolonged sensations of tingling, numbness, sense of movement, desire to move, or very occasionally pain. A detailed march may occur from one somatic part to the next one. It may spread so as to produce motor movement in the same member.

Visual seizures consist of lights, sometimes colored, or dimming of vision or blindness.

Auditory seizures are characterized by simple sounds, e.g., buzzing or drumming which are referred by the patient to the opposite ear.

Vertiginous seizures are frequently reported by the patient as dizziness or unsteadiness.

Olfactory seizures are also known as "uncinate fits" because of their localization to uncinate gyrus. Their chief feature is a disagreeable odor.

Visceral seizures—These seizures may be viscerosensory or visceromotor or a combination of the two. The sensory phenomena may be an epigastric aura, a sense of nausea, or a sense of oppression or fear. Under visceromotor phenomena may be listed pupillary, vascular, gastrointestinal and pilomotor reactions.

Psychical seizures—*Dreamy state seizures* include illusional or hallucinatory seizures. The illusional seizure is a rather sudden alteration of the patient's perceptions resulting in a sudden feeling of familiarity with the present situation, or of strangeness, or of being far away. Sometimes only one sense may be involved with sounds being louder or objects being altered in size. The hallucinatory seizure is more complicated and the patient is not aware of his surroundings or only partially so, resembling the dreams that occur in normal sleep.

TABLE 1

SPECIAL STUDIES ON A GROUP OF 108 PATIENTS WITH CONVULSIVE DISORDERS

	Total Tested	Abnormal		Remarks	
		Number	Per Cent	Findings	No. of Patients
SKULL X-RAY	87	16	18.4	Increased intracranial pressure	3
				Changes in dorsum sellae	3
				Bony defect	2
				Internal hydrocephalus	1
				Osteoma in inner table	1
				Hyperostosis of frontal bone	2
				Bilateral calcification of basal nuclei	1
				Bone defect or deformity	4
				Cholesteatoma	1
ELECTROENCEPHALOGRAM	51	35	68.6	Diffuse abnormalities	28
				Focal abnormalities	7
BLOOD SUGAR	62	0		All within normal limits	
GLUCOSE TOLERANCE TESTS	13	3	21.1	Bizarre curve	1
				Elevated curves	2
AIR STUDIES	46	13	28.3	Cerebral atrophy	6
				Space-occupying lesions	4
				Distorted ventricles	2
				Enlarged subarachnoid spaces	1
SPINAL PUNCTURE	69	5	7.3	Elevated protein	2
				Positive Wassermann	1
				Elevated colloidal gold curve	2
PSYCHOMETRIC EXAMINATION	68	40	57.7	1. Low I.Q. 2. Abnormal profiles on Minnesota Multiphasic Personality Inventory 3. Evidence of deterioration due to organic brain damage	

Forced thinking is an episode during which the same thought or idea repeats itself in an uncontrolled fashion and during which time the patient is out of contact with his environment. On recovery he is frequently able to recall the idea.

Stereotyped behavior consists of a prolongation of the activity in which the patient was engaged at the onset of seizure. The patient is unconscious during the episode and cannot recall his actions.

Petit mal is a term which should be reserved to describe short interruptions of the stream of consciousness. The patient learns of them from evidence of lapse of time. Observers note a vacant expression and perhaps a suspension of productive activity. The term is erroneously used when it is applied to any seizure of short duration.

Automatism is the state in which an individual does not have conscious control of activity. If it occurs after a seizure it is called *post-ictal.*

Psychotic states are actually post-ictal phenomena usually resulting from severe or repeated seizures over a long period of time. These patients are frequently very violent and often extremely dangerous during the episode.

It will be seen from the foregoing classification of clinical manifestation that unless the practitioner is aware of some of the nuances of these disorders, many cases could escape detection. Undoubtedly, there are considerably more cases of convulsive disorders than the 650,000 known to exist in the United States.

ETIOLOGY

Heretofore, too many cases have been relegated to the category of "idiopathic epilepsy" (or in the newer terminology "convulsive disorder due to unknown cause"). This group is a large one because symptoms often appear many years after the initial cerebral injury and therefore no apparent cause is elicited at the onset of the first seizure. A careful history, especially in reference to early trauma and infectious diseases, frequently brings out a forgotten source of brain damage. The electroencephalogram comes to our aid on this point. It has been shown rather frequently in our series of cases that the brain waves show a focus of abnormality indicating some previous damage to the underlying brain. Other records show evidence of diffuse cortical damage.

At present all our cases are being subjected to a careful Seizure History designed to bring out forgotten or overlooked factors of etiologic significance. The study of a patient for a convulsive disorder includes the use of various diagnostic procedures designed to aid further in bringing out causes of a patient's seizures. At the present time this workup includes the Seizure History, a neurologic examination, an electroencephalogram, a skull x-ray, fasting blood sugar (and if possible glucose tolerance test), psychometric examination, spinal puncture, and where indicated, a pneumoencephalogram. Table 1 indicates the results of some of these studies. Penfield and Erickson[1] have correlated the age of onset of seizure with the presumptive cause of the seizures.

Our data, which are now in the process of being analyzed, would indicate that the so-called cryptogenic or idiopathic convulsive disorder is relatively uncommon if one considers in detail the patient's early history and evaluates him carefully with the various laboratory procedures.

TREATMENT IN THE CONVULSIVE DISORDER

The average practitioner often considers drug therapy as constituting the sole method of attack on the convulsive disorder. This has time and again been proved to be a narrow and often inadequate approach. In reference to our original definition it is found that the convulsive disorder is predicated on an excessive discharge of neurons. This excessive discharge is precipitated by various external and internal factors. Any rational system of therapy will include the elimination of factors which are known to increase the frequency of seizures. Such factors are anxiety, frustration, tension, excessive fatigue, irregular or inadequate meals, excessive hydration, and exposure to the toxins, e.g., alcohol and carbon monoxide. The emotional reaction of the patient caused by his attitude and that of others toward his illness is probably the most important factor in the precipitation of seizures and is the most difficult to rectify. In addition to the removal of the above contributing factors, drug therapy is used for the chemical suppression of the excessive neuronal activity. An adequate therapeutic regimen then can be outlined as follows:

Psychotherapy—In a narrow sense the therapist engages in psychotherapy on an individual basis, depending upon the symptoms requiring alleviation by certain simple and generally applicable technics such as reassurance, explanation, ventilation, etc. In a broader sense it means education of the patient and his family. There exists an organization called the American Epilepsy League which was founded in 1939. This organization, which has many local chapters, acts in an advisory and educational capacity. It is an organization of laymen designed to improve the lot of the patient both by his education and that of the general public. The patient should be referred to the local chapter of this organization so that he may benefit by the educational program.

Another psychotherapeutic measure of general nature is the occupation of the patient either in gainful employment or school work. Most of the employed patients have their jobs because the existence of their illness is not known by the employers. Insurance companies do not care to assume the alleged excess risk presented by a patient with convulsive disorder. No legal provision exists in most states, whereby a patient with a convulsive disorder may sign a waiver releasing the insurance carrier of liability in the case of injuries due to his disability. There are actually few work restrictions required. The outstanding of these are the driving of automobiles and similar vehicles and the operation of certain types of machinery. It is felt by at least one clinic that all restrictions should be removed in the case of a patient who has been controlled for a year.

Diet—The patient should have his meals at a regular time, and they should consist of a well-balanced diet.

Avoidance of excessive fatigue—This should be accomplished through regular and adequate rest or sleep and the avoidance of work beyond the individual's physical or intellectual capability.

Avoidance of toxins—The chief offender in this group is alcohol. Abstinence from alcoholic beverages is required. There are also industrial poisons, e.g., carbon monoxide in garage work. The patient should not engage in occupations where these are a hazard. The imposition of toxins on neurons which are already functioning improperly is not considered wise.

Dehydration—Our procedure is to limit fluids to approximately 1,000 cc. per day. The rationale behind this procedure is based on the concept that an excessively hydrated brain has a lowered threshold for seizures.

Surgical treatment—Surgical approach in the

TABLE 2
SUMMARY OF RESULTS WITH DRUG THERAPY

Drug	Total Number of Patients	Controlled		Improved		Not Controlled		Toxic Symptoms		Controlled or Improved	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Phenobarbital	65	34	52.3	17	26.0	14	21.5	15	23.0	51	78.3
Mebaral	71	38	53.5	16	22.5	17	24.0	5	7.0	54	76.0
Dilantin	42	16	39.0	9	21.4	17	40.5	11	26.2	25	60.4
Mesantoin	25	11	44.0	5	20.0	9	36.0	9	36.0	16	64.0
Phenobarbital and mesantoin	1					1		1			
Phenobarbital and dilantin	11	5	45.4	2	18.0	4	36.3	3	27.2	7	63.4
Mebaral and mesantoin	12	4	33.3	4	33.3	4	33.3	2	16.6	8	66.6
Mebaral and dilantin	28	15	53.6	9	32.0	4	14.2	4	14.2	24	85.6
Total in which drug therapy was used	255	123	48.2	62	24.3	70	27.4	50	19.6	185	72.5

case of neoplasms and other operable conditions is obvious. In recent years at least two centers have engaged in extirpation of cortical areas considered to be the foci of seizures. This work is done on such a small scale that it is not generally applicable to the management of convulsive disorders. It has been mentioned for the sake of completeness.

Drug treatment—Before beginning a discussion of the drug therapy in the convulsive disorders, it is important to re-emphasize that drug therapy is only a part of the total treatment of convulsive disorders. Frequently, it is the neglect of this fact that results in dissatisfaction to both the physician and the patient. It cannot be too strongly emphasized that the convulsive disorders cannot be satisfactorily handled simply by supplying the patient with a prescription for anticonvulsant medication.

The regulation and control of the patient's medication is an individual problem. One must not only find the drug or combination of drugs which will give the best results, but one must frequently alter the drug schedule to fit the shifting needs of the patient. For example, many female patients require a different drug routine during the phase of their menstrual cycle, the usual change being an increase of medication during menstruation.

Frequent changes are often necessary to compensate for the increased tendency to attacks during periods of increased emotional tension. For example, one of our patients found it necessary to double the amount of his medication whenever he spoke before his sales organization. Many patients notice a greater tendency toward side reactions from their medication when they have colds or other febrile illnesses. Such reactions naturally must be compensated for in the drug routine. This is of importance particularly in individuals given large doses of medication—amounts which are just under the threshold of toxicity.

RECOGNIZING these factors in the medicinal treatment of the convulsive disorders, it becomes apparent that an intimate knowledge of the comparative value of each drug in the various types of the convulsive disorders is most essential to a proper handling of these patients. Consequently, the following study was instituted in an attempt to compare the value of the different available anticonvulsives. Each of the drugs was given to the same group of patients. The use of the same patients enabled us to compare the effect of each drug under fairly similar circumstances. In each patient of this series an attempt was made to obtain the best possible seizure control with one drug before changing to another. Thus, each patient in the series had a trial with each drug until maximum benefits were obtained or until he showed toxic symptoms from the drug.

Before presenting our material, it might be appropriate to mention the anticonvulsive drugs now available, their method of administration, and the possible toxic effects from overdosage. No mention can be made of routine dosage since there is no standard dose of any of the drugs used in this condition. The actual dosage can only be defined as that amount of drug which is necessary to produce the best control effect without or with a minimum of undesirable toxic symptoms.

(1) *Bromides* were some of the first drugs used

TABLE 3
COMPARATIVE RESULTS ON 25 PATIENTS

	Controlled	Toxic or not controlled
Phenobarbital	6	19
Mebaral	16	9
Dilantin	7	18
Mesantoin	15	10

in the control of convulsive disorders. Bromides were introduced by Sir Charles Locock in 1853.[2] Although bromides have been replaced by newer medications (chiefly barbiturates and hydantoins), they are still useful in many individuals. Many obstinate cases may be brought under control with a proper combination of bromides and barbiturates. The common toxic effects of bromides are skin reactions and drowsiness. Long continued use may result in the development of a toxic psychosis.

(2) *Phenobarbital* was introduced by Hauptmann[3] in 1912. This drug soon became, and continued to be, the treatment of choice until very recently. The common side effects are drowsiness, skin reactions, and gastrointestinal disturbances. Drowsiness is by far the most common and disturbing reaction.

(3) *Mebaral,** a preparation of mephabarbital, is supplied in ½ gr., 1½ gr., and 3 gr. tablets. In our clinic we have found that this drug produces a minimum of undesirable reactions, even in large doses. The side reactions, when they occur, are similar to those of phenobarbital.

(4) *Dilantin,* diphenylhydantoin sodium, was introduced by Putnam and Merritt[4] in 1937. Dilantin is supplied** in ½ gr. and 1½ gr. capsules. The side effects are tremor, dizziness, restlessness, ataxia, skin reactions, gastrointestinal symptoms, and hypertrophy of the gums. Many patients can take dilantin for many years without untoward symptoms and then rather rapidly develop a severe ataxia which subsides when dilantin is withdrawn.

(5) *Mesantoin,* 3-methyl 5, 5 phenylethyl-hydantoin, was first reported by Loscalzo[5] and Kozol[6] in 1945 and 1946. Mesantoin† is supplied in 1½ gr. tablets. Its side reactions resemble those of dilantin and consist of tremor, dizziness, drowsiness, ataxia, skin reactions, gastrointestinal symptoms, blood dyscrasias, and a curious manifestation which resembles a febrile illness with adenopathy. In cases where drowsiness is the predominant symptom, it can frequently be relieved by the administration of dexadrine sulfate. It is recommended that patients on this medication have monthly blood counts.

The above mentioned drugs are all useful for the control of major seizures and, with the exception of Mebaral, are of little value in the control of minor seizures. For the control of the latter, in addition to Mebaral, one can use the following:

(6) *Tridione,* 3, 5, 5, trimethyloxazolidine-4, 4-dione, was introduced by Lennox[7] in 1945. It is supplied in 4½ gr. capsules.‡ Its most characteristic toxic symptoms consist of photophobia, skin reactions, and gastrointestinal symptoms. A rare and disturbing toxic effect is the development of an aplastic anemia. For this reason repeated blood studies at least every two weeks are indicated in any patient placed on this drug. It must also be kept in mind that occasionally Tridione will precipitate grand mal seizures even though the minor seizures are controlled. For this reason one of the drugs controlling major seizures must always be given with the Tridione.

(7) *Glutamic acid* has been used in the control of minor seizures,[8] but since large doses of medicine are necessary and since its action is unsustained, the therapeutic value of this drug is of doubtful worth.[9]

It is a well known fact that different combinations of the above mentioned drugs are frequently much more effective than any single drug.

Results of our investigations with drug therapy can be summarized as follows:

DRUG THERAPY

TABLE 2 shows the results of our drug therapy in the total number of 108 patients treated up to the present time. Many of these patients have been placed upon different combinations of the drugs. As will be seen from the table, by far the most favorable results were obtained from the use of phenobarbital and Mebaral. In each of these drugs approximately 75 per cent of the patients were controlled or definitely improved. However, in this group of patients the phenobarbital produced a much higher percentage of toxic symptoms than did the Mebaral. It is for this reason that we have preferred the use of Mebaral.

From our experience we have been impressed

*Brand name of Winthrop-Stearns.

**Parke Davis and Company.

†Sandoz.

‡Abbott Laboratories.

TABLE 4
TOXIC REACTIONS IN DRUG THERAPY

	Drowsiness	Gum Hypertrophy	Lymphadenopathy	Rash	Tremor	Ataxia	Totals
Phenobarbital	19						19
Mebaral	7			2			9
Dilantin	1	2		1	8	6	18
Mesantoin	1		1	3	2	3	10

by the results that can be obtained by the combined use of the anticonvulsants. By the addition, for example, of Mebaral to Dilantin, one can obtain 85 per cent control or improvement in patients with convulsive disorders. One criticism of this table is the fact that many more patients were treated with phenobarbital and Mebaral than with the hydantoins. This discrepancy in the number of patients treated by the individual drugs tends to make a specific comparison of these medications somewhat questionable. An attempt has been made to correct this weakness in Table 3 where the individual drugs have been given to the same patients and where a specific comparison is possible.

Table 3 is a comparison of the four most commonly used drugs in the convulsive disorders when given to the same group of patients over a period of years. Obviously when the different drugs were tried with the same group of patients, one has the most ideal conditions in which to evaluate their efficiency. The greatest difficulty in setting up such a controlled experiment, however, is the fact that it is almost impossible to follow a large series of such patients over the number of years required for an adequate evaluation of a series of drugs. To date we have been able to follow through such a study on 25 patients (Table 3). As will be seen from this study, the best results were obtained from Mebaral and Mesantoin. However, in view of the greater severity of the toxic effects of Mesantoin and in view of the relative ease with which Mebaral can be administered to most patients, it would appear that this drug at the present time is one of the best for the treatment of the convulsive disorders in general.

Finally, Table 4 is a listing of the relative frequency of the different types of toxic symptoms resulting from the anticonvulsive medication used in our test group of 25 patients. By far the most frequent toxic symptom was lethargy or drowsiness which was produced predominantly by both phenobarbital and Mebaral. Aside from the drowsiness the majority of the toxic symptoms resulted from the use of the hydantoins (Mesantoin and Dilantin) and consisted of tremor, ataxia, and a severe skin rash. The ataxia may be of such intensity as to incapacitate the patient completely. The rash may be so severe as to require hospitalization for a long period of time. One of the peculiarities of this hydantoin toxicity is the fact that these symptoms tend to regress very slowly and may be distressing to the patient for a long period of time.

The case of lymphadenopathy resulting from Mesantoin is of sufficient interest to warrant a more detailed account. The patient after being on Mesantoin for two weeks developed fever and lymphadenopathy. Microscopic sections of the enlarged lymph nodes were indistinguishable from those obtained in Hodgkin's disease. The patient recovered on withdrawal of Mesantoin. Inadvertently, he again took Mesantoin and developed fever, rash, and lymphadenopathy. He subsequently recovered on withdrawal of the drug. Another of our patients, not part of the group in Table 4, while taking Mesantoin developed an anemia. A bone marrow biopsy closely resembled that obtained from patients with leukemia.

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Diagnostic Clinic

Cancer of the Urinary Bladder

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We have heard a great deal about cancer during the last two or three days. I am going to continue the discussion of this subject, but I am going to take you underground, anatomically speaking, to the urinary bladder.

I will recite my conclusions first, so that if I run out of time during the clinical demonstration, I will have given you my opinions based on the data that appears here in my published paper.

We have several patients to present to you who have been brought here by Drs. Higgins and Horton of the Cleveland Clinic. All have had some method of treatment for carcinoma of the urinary bladder. It is impossible for you to peek through the cystoscope or to look through a surgical incision into the urinary bladders of these patients. Their appearance here is sufficient evidence that they have had treatment for cancer of the urinary bladder and have survived.

CONCLUSIONS

1. Cancer of the urinary bladder caused 3.2 per cent of all cancer deaths during the last ten-year statistical period.

2. Morbidity and mortality rates have not lessened. Most surgeons are too conservative when treating cancer in this anatomic area.

3. Microscopic and macroscopic blood in the urine means cancer in the urogenital tract; often in the urinary bladder. Complete urologic examination must be done at once to locate and determine the cause of bleeding. Recurrence of bleeding may not occur for several months, during which time spread of cancer and metastases may occur.

4. Heretofore, the *diagnostic methods* employed to reveal the presence of malignancy in the urinary bladder and its grade *have not been accurate. All tumors of the urinary bladder are malignant. No tumor is better than its worst part.*

5. Bimanual palpation, under anesthesia when necessary, will reveal useful information concerning the character of bladder tumors and their extension to perivesical structures.

6. When in doubt, surgical exploration is frequently necessary to obtain *an accurate diagnosis* of (a) the presence of malignancy, (b) the presence and extent of local spread, (c) the presence and extent of abdominal metastases, and to plan and begin the steps incident to radical surgical treatment, as diversion of the urinary stream preparatory to cystectomy.

7. Transurethral operations should be done only for Grade I malignancy, and when no spread or metastases are evident. If local recurrences occur, subsequent to transurethral resection, radical surgery may be indicated at once.

8. When palliative treatment is necessary, diversion of the urinary stream produces more comfort to the patient and also permits better control of the local mass.

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GILBERT J. THOMAS

9. All tumors of the urinary bladders are cancers. Let us do away with our conservatism and procrastination and try to cure them *by early, accurate diagnosis and early radical treatment.*

Lack of improvement in the morbidity and mortality associated wtih carcinoma of the urinary bladder has been due in many instances to inaccurate diagnostic data, and the mode of surgical therapy which has not always aimed at cure by complete surgical removal of all of the cancer and the cancer-bearing tissue.

ETIOLOGY

Little is known about the exact causes of cell and tissue changes in the mucosa that develop into malignant tumors. Animal experiments, together with clinical research and observation, suggest that mechanical and chemical irritation play some part in the formation of malignant tumors. The occurrence and growth of spontaneous bladder tumors may bear some etiologic relationship to continuous contact of the mucosa by urine containing unrecognized chemical carcinogenic agents encountered by workers in the analine dye and other industries. Forty-one per cent of bladder tumors are found on the floor, where *trauma,* produced by the constant presence of urine that may contain carcinogenic substances, may be an additional etiologic factor in stimulating cancer cell production in this area.

Arsenic was recovered from an ureteral papilloma in a patient who ingested large quantities of this material in the form of Fowler's solution.

Most pathologists recognize a carcinogenic predisposition on the part of the cellular structure of some or all tissues of the urinary bladder and other urogenital organs. Papillomata of the bladder mucosa that recur suggest continuing activation of the predisposed cells to carcinogenic agents within the urine or the blood stream. *I think that this observation is very important.*

Figure 1 reveals the presence of a tumor in the bladder and at the bladder end of the ureter and one in the kidney pelvis. While we are viewing this illustration, I want to emphasize my opinion, and that of most urologists who now believe that multiple tumors in the genitourinary tract are not transplants of tumor cells from a tumor in the pelvis of the kidney to lower areas as the ureter and bladder. We are dealing here with multiple tumors that are produced any place on the epithelium of the urogenital tract because the cells in these tissues have a carcinogenic predisposition and are activated by some carcinogenic stimulators within the urine.

Dr. Thomas Kerwin of New York is convinced that papillomas of the urinary bladder are due to a filterable virus.

Another etiologic feature that must be kept in mind when considering tumors of the bladder that are found on the trigone and extend into the prostatic urethra is the possibility that these tumors, as those originating in the prostate gland, *may be gonad related.* Some urologists have reported excellent results when estrogenic substances were used parenterally, together with other methods of treatment in male patients who had cancers of the bladder extending into the prostatic urethra.

Cancer in man then is to a considerable extent an environmental and occupational disease.

SYMPTOMS

When no other lesions are present in the urinary bladder, the first symptom or finding that one notices with carcinoma is *hematuria.* Hematuria is usually painless unless the tumor is

located at the bladder neck or accompanied by severe cystitis, hyperplasia of the prostate gland, or the presence of a foreign body within the lumen of the bladder. *Microscopic blood cells* in the urine observed by the physician may be the first and the only finding. The presence of these cells in any patient's urine is a positive indication for immediate complete urologic examination, which must include clear pyeloureterocystograms.

Hematuria is the cardinal symptom in 91 per cent, the initial symptom in 70 per cent and may be present in persons of any age. The average age of cancer is 57; the average when infection is present is 39. Cancer in the upper genitourinary tract produces hematuria in 70 per cent; in the lower tract, 30 per cent. Fourteen per cent of all admissions to the urologic services in large clinics was because of the presence of blood in the urine. Of all patients complaining of hematuria, 4 per cent will have some general disease; 96 per cent because some lesion is present within the genitourinary tract; and 20 per cent of these will be caused by cancer within the urinary bladder.

EARLY DIAGNOSIS

When the urologist begins the search for the cause of hematuria, he must think of the lesions and conditions that are revealed in Figure 2. From this you can see what a problem proper diagnosis may be. The urologist must make a complete thorough examination of the entire genitourinary tract.

What is the general practitioner or surgeon going to do when he examines a patient who has hematuria? Are there examinations that he can make that will be helpful to him?

First, this patient should be thoroughly examined for evidence of general diseases as these may cause hematuria in 4 per cent. The examining physician can make an x-ray examination of the whole urogenital tract, including an intravenous urogram, and then through an urethral catheter shadow-casting material may be introduced into the bladder lumen when anterior, posterior, and lateral views of the filled urinary bladder may be obtained (Figure 3). When a large bladder tumor is present, the deformity is very easily seen on the film. When smaller ones are present, if the examiner will remove the shadow-casting material from the bladder with a catheter, a filling defect may occur where the remaining shadow-casting material has clung to the tumor. Filling defects in the cystogram may be caused by conditions other than a tumor of the urinary bladder.

Hematuria may be caused by a carcinoma of the bladder associated with hyperplasia or carcinoma of the prostate gland. It is my practice, when dealing with hyperplasia of the prostate gland with associated hematuria, to pass a cystoscope or endoscope so that I may observe the interior of the bladder. In several instances I have found unsuspected carcinoma of the bladder that was the cause of the hematuria; not the hyperplastic prostate gland.

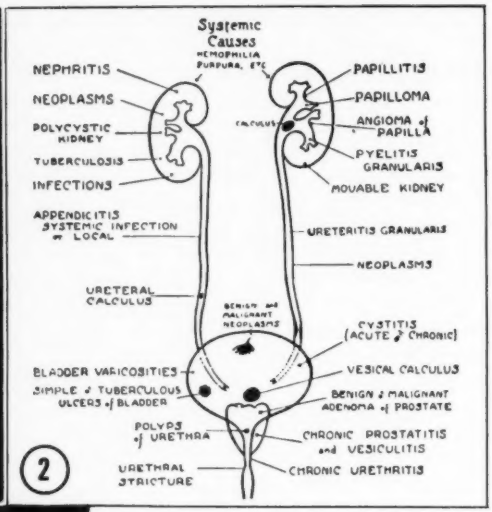
Another method of examination which is always at hand, as far as the general surgeon or general practitioner is concerned, is the bimanual examination of the bladder area which may require anesthesia. When the tumor is large enough to palpate, we must determine whether it is fixed and has invaded the bladder wall and the structures surrounding.

Suspected lesion in the bladder should be viewed through the cystoscope. At this time sections of the tumor may be removed for microscopic study, and the condition of the upper urinary tract must be appraised because frequently lesions are present in other areas of the mucosa of the urogenital tract in addition to those in the bladder.

After the introduction of the cystoscope through the urethra and into the bladder, the tumor is located in relation to the ureteral orifices and other anatomic structures. After identifying the presence and location of the tumor, its character must be determined. This may be accomplished when it is possible to obtain a clear view of the entire tumor, its attachment to the bladder wall, the condition of the bladder mucosa adjacent, the presence of sloughing in the tumor, and bleeding.

Carcinoma of the bladder may obstruct the outlet of the ureter to the bladder. Carcinoma may be present within a diverticulum of the bladder (Figure 4), so that the careful examination of the bladder mucosa, and when possible, the introduction of the cystoscope into diverticuli, may be necessary. Through the cystoscope the urologist can visually inspect a tumor and may determine its character, but he cannot see how far it has invaded through the bladder wall as he can see the mucosa only. However, a trained cystoscopist can make an accurate diagnosis of the presence of malignant change and its grade.

The drawing of a bladder tumor (Figure 5), which has been made by Dr. Melicow, reveals the reason for the inaccuracies in the diagnosis of



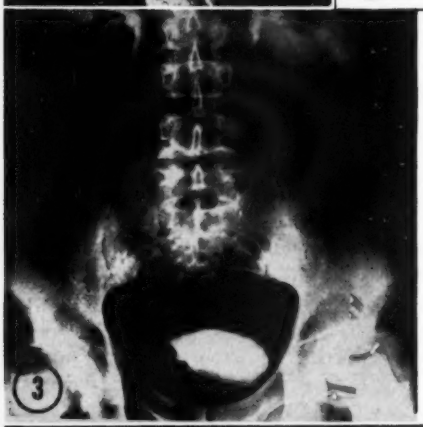
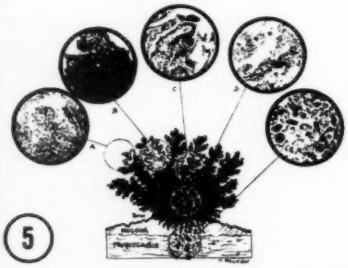
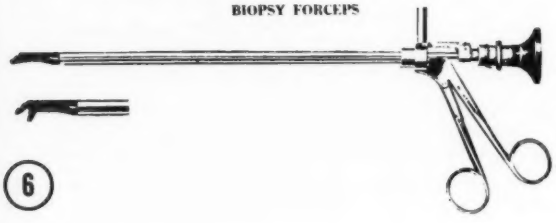


FIGURE 1. Multiple tumors of the kidney, pelvis, ureter, and bladder not a transplant from the renal pelvis. FIGURE 2. Pathologic conditions in genito-urinary tract that may produce hematuria. FIGURE 3. Pyeloureterocystogram. Deformity and filling defect in urinary bladder. Normal renal pelvic shadows. FIGURE 4. Carcinoma within a diverticulum of the bladder. Destruction of kidney on this side. FIGURE 5. Histopathologic structure of bits of tissue removed from various areas of a tumor of the bladder. The most malignant bit of tissue was removed from the attachment of the tumor to the bladder wall. (Melicow.) FIGURE 6. Tissue may be obtained under vision. (Telescope passes through shaft of instrument.)





the presence of, and the degree of, malignancy that may occur when bits of tissue are removed from various parts of a tumor transurethrally.

The removal of bits of tissue through the cystoscope is accomplished by specimen takers and rongeurs that are passed through the sheath of the cystoscope or of the resectoscope (Figure 6). The specimen must be removed from the area of the bladder wall to which the stalk of the tumor is attached. Specimens are obtained when the jaws of the instrument are closed. Some rongeurs contain a telescope so that bits of tissue may be removed under direct vision.

The *resectoscope* removes sections of tissue because it contains an electrically activated loop which destroys adjacent tissue as it removes it.

Figure 7 illustrates one of the transurethral methods of removing bits of tissue for microscopic study that is inaccurate. One section in the photograph of the microscopic section was removed by the cutting current of the *resectoscope*. One can see that the tissue has been destroyed so that the pathologist cannot identify the cellular structure of this tissue. On the other half of this illustration is a microphotograph of a bit of tissue removed surgically from the same tumor. There is evidence of malignant change in this tissue.

In the next illustration (Figure 8), I show you microphotographs of bits of tissue that were removed through the endoscope with a specimen-taking instrument and via open surgical operation. One reveals a cystic condition that is not considered malignant as it is viewed through the microscope. In the other, however, you see that there is very definite malignant change, Grade III to IV. If one had depended on the tissue removed with the rongeur, or the specimen shown here on the left, one would say that we were dealing with a nonmalignant lesion of this bladder.

A fibrous papilloma is shown in Figure 9; the epithelium can still be seen. The whole mass is fibrous in character; it protrudes into the lumen of the bladder, but when it was removed surgically, it was found to be definitely malignant.

Another illustration (Figure 10) reveals a Grade I malignancy which ordinarily would be called a papilloma. The tissue from this tumor was removed through the cystoscope. When this bladder mass was examined surgically and biopsy made from the bladder wall, we found a Grade III malignancy.

I discussed these apparently contradictory diagnostic data with Dr. J. R. McDonald, pathologist from the Mayo Clinic, who, in this clinic, pays particular attention to lesions that occur in the urogenital tract. I voiced the opinion that the urologist was not correct in depending entirely upon the pathologist's report concerning his examination of bits of tissue that were removed through the cystoscope. He was in agreement that bits of tissue removed in this manner were not always satisfactory specimens for microscopic study.

In his opinion, the pathologist did not always give the urologist all the information that he should after he had examined bits of tissue from a tumor of the urinary bladder. Dr. McDonald believes that the pathologist should report the types of carcinoma cell, whether squamous, adenoma, transitional; he should report the character of the tumor, is it papillary, with or without infiltration, or just infiltrative; and the pathologist must report a very important finding—has vascular invasion occurred?

Dr. Archie L. Dean of New York, who has had wide experience with diagnosis and treatment of carcinoma occurring in the urinary bladder, reported recently that in 58 per cent, the microscopic examination of the entire bladder tumor differed from the diagnosis that was made of the biopsy specimens removed preoperatively through the cystoscope. In 50 per cent of the patients operated on, the examination of the whole tumor revealed a higher degree of malignancy than that found during examination of cystoscopic biopsy specimens.

It is my opinion that the trained cystoscopist who has observed many tumors of the urinary bladder and has subsequently examined both the biopsy and surgical specimens, can make a more accurate diagnosis of the presence of malignancy and its grade from his cystoscopic observation than the pathologist who must depend entirely upon his examination of a bit of tissue obtained through the cystoscope. The experienced urologist will evaluate all the characteristics of a tumor that may be observed through the cystoscope—does it have a small pedicle? is there evidence of infiltration? does it have a sloughing top? does it bleed easily? what is its shape? what is the character of the bladder wall adjoining?

PROGNOSIS

In a study of the results of pathologic changes that occurred in 107 cases of infiltrative carcinoma

made to determine conditions under which local extension and metastases occurred, Dr. Jewett found the following: In Group 1, comprising 3 cases, the deepest penetration into the bladder wall was at the submucosa. In this group no evidence of spread could be observed. In Group II, which comprised 15 cases, the growth extended into, but not through, the muscularis. Eighty-six per cent of this group were free from evidence of spread. In Group III, or 89 cases, the growth had penetrated through the muscular layers. Only 26 per cent revealed no evidence of spread.

Since potential curability can be considered to exist whenever no spread has occurred, the drop in curability after the perivesical tissue has been reached is statistically significant. Dr. Jewett observed that metastases were less frequent when the tumor was located in the posterior wall of the bladder. Recently Dr. Jewett has divided his Group III above into two sub-groups: sub-group A being tumors which have invaded only part way through the muscle, and sub-group B when the perivesical tissue has been involved.

These data reveal the reason for our being accurate in our preoperative diagnosis. We must not subject patients to radical surgery if there is no hope of removing all of the cancer so that cure can be expected.

METHODS OF TREATING CARCINOMA OF THE BLADDER NOW USED

When we are sure we are dealing with a Grade I malignancy, a single tumor with a small stalk, with no evidence of extension or metastases, this may be treated by electrocoagulation with the electrode of the diathermy machine that is passed through the cystoscope. For larger tumors that are thought to be nonmalignant, or Grade I malignancy, the resectoscope is being used. This is the instrument that was made primarily for the removal of sections of the prostate gland transurethrally.

The resectoscope may be used not only to remove the tumor but also to resect sections of the bladder wall adjacent to the stalk. There is some danger in using this instrument as it may penetrate the bladder wall. Here, as with the endotherm, we do not know how deeply the resection must go as we cannot see how deeply the tumor has penetrated. In my opinion, the resectoscope is being used too frequently in the treatment of cancer of the bladder. The tumor may be entirely removed as far as one can observe through the resectoscope. I think that when the endoscopist observes a tumor of more than Grade I malignancy, segmental or radical resection of the bladder should be practiced. The use of the resectoscope for this purpose is surgical procrastination and has interfered with our attempt to cure cancer of the bladder by complete removal of the tumor, and the bladder, in many instances.

During the last year I examined the data in the histories and operative reports of 31 patients suffering with carcinoma of the bladder that we had taken care of in our institution. This survey was done to see how frequently we had made a wrong diagnosis and how often we had applied palliative treatment when radical treatment was indicated.

The number of cases of Grade I malignancy was 7. All were treated through the cystoscope or by transurethral resection. There were 6 recurrences, 3 with increased grade of malignancy when the tumors were surgically removed. Six were obviously incurable and inoperable at first examination. There were 5 with multiple cancers—3 in the prostate gland—and 2 in the kidney or ureter. Four cases were considered operable and cure possible. We procrastinated by cauterizing and resecting 3 bladder tumors when not sure of the diagnosis. There were 6 operative deaths in this group (18 per cent). This gives you some idea of the seriousness of carcinoma of the bladder and why it is necessary for us to make an accurate early diagnosis and apply radical surgical treatment if we expect to cure these individuals.

One of the cancers occurring in one of my cases last year deserves mention. Here procrastination led to spread of a very serious incurable cancer in the bladder. When we first saw this patient a diagnosis of *leukoplakia* had been made elsewhere (Figure 11). The condition had been watched and was frequently fulgurated through the cystoscope. The primary area was diagnosed as leukoplakia and nonmalignant. Later it developed into a squamous cell tumor that was very malignant. We removed this patient's bladder and did a cutaneous ureterostomy. There was, at the time of surgery, no evidence of metastases or spread to other surrounding structures. Shortly thereafter evidence of local spread and metastases was present (Figure 12).

When patients have transurethral removal of the tumors of their bladder, we insist that they return for cystoscopic examination every three months the

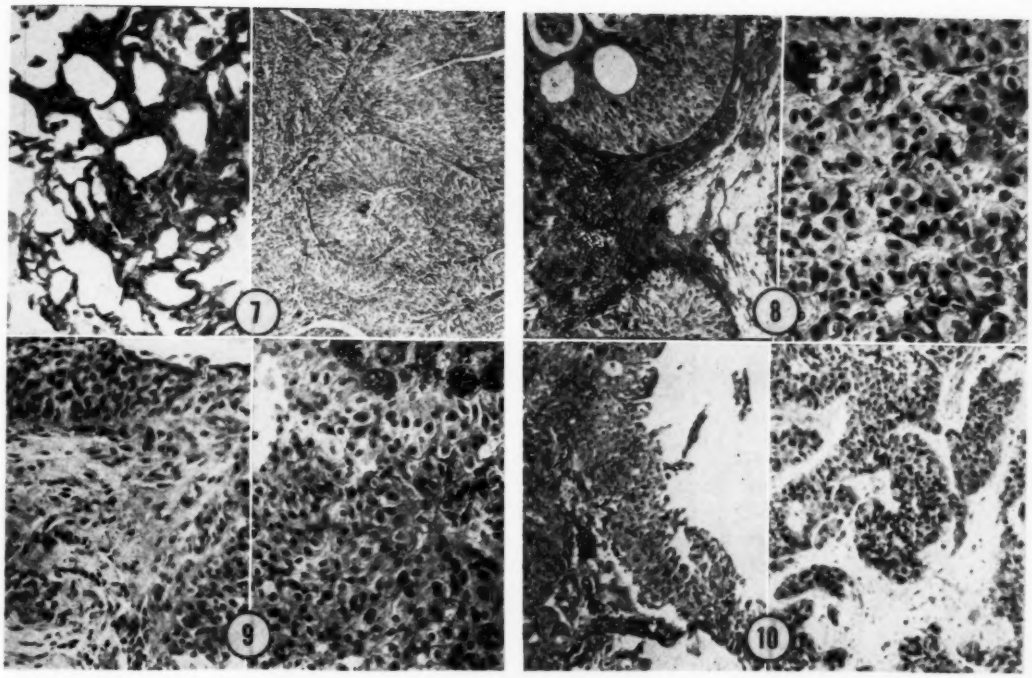


FIGURE 7. Biopsy specimen obtained by cautery. Diagnosis impossible. Same tumor bit removed at operation, papilloma. (Melicow.)

FIGURE 8. Bowenoid disease not considered malignant. Surgical specimen infiltrating anaplastic epithelioma, Grade IV. (Melicow.)

FIGURE 9. Biopsy fibrous polyp; at operation epithelioma, Grade II. (Melicow.)

FIGURE 10. Biopsy papilloma, Grade I. Surgery infiltrating epithelioma, Grade III. (Melicow.)

FIGURE 11. Leukoplakia bladder five years before surgery.

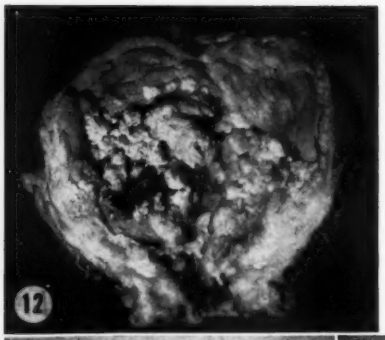


FIGURE 12. Squamous cell cancer of bladder, prostate gland, etc.

FIGURE 13. Tube grafts ready for implantation of ureters.

FIGURE 14. Ureters in grafts. Bladder removed.

FIGURE 15. Total destruction of kidney and ureters. No treatment applied. Ureters not transplanted.

first year, and every six months the second year, and once a year for the next two or three years. We do this to be sure we have controlled the condition found in the bladder. We may treat minor recurrences by the transurethral route. If multiple recurrences occur, cystectomy should be done.

Elsewhere in this discussion I mentioned the possibility that many tumors of the base of the bladder may be gonad related and may extend into the prostate gland. We feel that it does the patient no harm, and many urologists have reported very excellent results from the use of estrogen parenterally as an adjunct treatment for tumors of the bladder that involve the prostate gland and prostatic urethra.

The method we use of implanting the ureters into the skin when it is impossible to do a ureteroenterostomy is illustrated in Figure 13. The plastic surgeon makes a tube graft in the proper position on the anterior abdominal wall. When this is completely healed so that the tube graft sticks out from the surface of the skin of the abdomen like the tit of a cow's udder, we then dissect the ureter free, and after making a hole through the tube graft from without in, we pull the ureter through this tit-like projection of the abdominal wall. The mucosa of the ureter is sewed to the skin edge of the teat and the wall of the ureter is sewed to the abdominal wall. By this method we make a controllable exit for the ureter (Figure 14). Bags and other types of apparatus that are used to catch the urine do this better with this tit-like projection. When catheters are put into the ureters, these seem to drain better without leakage. An instance of total destruction of kidney and ureters is shown in Figure 15. No treatment was applied and the ureters were not transplanted.

I would like to present the patients now. Dr. Horton will give you a resumé of each patient's history, the pathologic condition present, and the

surgical treatment which was applied in each case.

DR. HORTON: The first patient is a 78-year-old man with a diagnosis of papillary transitional cell carcinoma of the bladder, Grade I. In May of 1945, he had transurethral resection of a bladder neoplasm plus implantation of radon seeds. He was examined every three months and was free of recurrences until approximately six months ago, at which time recurrences were found. These have been treated by fulguration.

DR. THOMAS: This gentleman had a Grade I malignancy. I talked about the diagnostic features of this case with Dr. Higgins, and we discussed my opinions about treatment for cancer of the bladder and the methods of diagnosis to be employed, with which he agreed. This man had a Grade I malignancy. He had fulguration and implantation of radon seeds. Nevertheless, there have been some recurrences. I wonder, in this case, if it would not have been better when the first recurrence occurred to transplant the ureters and remove the bladder. This man's cancer is spreading; however, he is all right now, and you can see that he looks like a pretty healthy individual.

DR. HORTON: This is a 71-year-old man with a biopsy diagnosis of papillary transitional cell carcinoma of the bladder, Grade II. In October, 1948, we performed a transurethral resection of the bladder tumor, plus radon seeds.

DR. THOMAS: This is another instance of the transurethral method of treatment in a patient in whom the diagnosis was accurate and thorough. This is the method of treatment to be used in this case.

DR. HORTON: The next patient is a 66-year-old man with a diagnosis of transitional cell carcinoma of the bladder, Grade II, made in April, 1947, at which time a subtotal cystectomy with reimplantation of the ureter into the bladder was performed. That was on the left side. Repeated cystoscopic examinations at three-month intervals have failed to reveal a recurrence since that time.

DR. THOMAS: In other words, here is an individual in whom open surgery was done, the area containing the cancer was completely removed, the end of the ureter sacrificed, the ureter reimplanted into the bladder, and he is free of tumor at the present time. How do you feel?

PATIENT: Fine.

DR. THOMAS: Any difficulty urinating?

PATIENT: No.

DR. HORTON: This man is 55 years of age. A diagnosis of a transitional cell undifferentiated carcinoma of the bladder, Grade III, was made in April, 1948. In August a right ureterosigmoidostomy was performed, and in September, 1948, a left ureterosigmoidostomy and complete cystectomy with block dissection of the iliac glands was performed.

DR. THOMAS: This is an instance where radical surgery was done, the type of treatment that I believe is most applicable for cancer of the bladder, except for Grade I, noninfiltrating, single malignancies. This man has had his bladder removed and his ureters transplanted into the bowel. He does have frequency of bowel evacuation two times a night. He complains a little bit that he has not been able to gain weight, but he looks pretty good, and as far as we can find, no recurrences have occurred.

I want to call attention to an item of surgical technic that Dr. Higgins employs that most urologists do not use. He resects the nodes along the blood vessels within the bony pelvis.

BEFORE radical surgery is undertaken, we explore the bladder, the pelvis, abdomen, and contents. We want to ascertain the presence of a cancer of the bladder, how far it has extended, whether metastases have occurred, and that the patient has a good chance of recovery from an operation of this magnitude, and that all the cancer will be removed. At the exploration we put the ureters into the bowel and subsequently remove the bladder.

This man has had that done and is getting along pretty well. I have told him that he can be encouraged because I have 3 or 4 patients now who have their bladders out and are recovering. We think this man is free of his cancer.

I want to emphasize again that open surgery is the best method of treatment, i.e., complete removal of a tumor of the bladder wall and sometimes the bladder. The best method of palliation is implantation of the ureters, either into the bowel or skin. This removes the carcinogenic stimulators that are in the urine so that many tumors of the bladder that could not be removed surgically have been controlled; some have reduced in size, after diverting the urinary stream. That is an important observation and I think it bears on the etiology of cancer of the transitional type that we see most often in the tissues of the bladder. Transplanting the ureters into the bowel or into the skin is an im-

portant palliative measure which I want to emphasize.

Newer methods of ureteral transplantation into the bowel are being used. The implantation is accomplished faster and easier with less ureteral obstruction that usually follows, and frequently without the infection that ascends into the pelves of the kidney. We know that diversion of the urinary stream has added many comfortable months of life to these chronic sufferers with cancer of the bladder when surgical removal of the entire bladder could not be done.

I feel that the operation of diversion of the urinary stream and cystectomy should be done in two stages. First, make an accurate diagnosis and look for metastases by surgical exploration. At the same time observe the extent of the tumor and how much surgery you have to do to remove it completely. Then do ureterosigmoidostomy or cutaneous ureterostomy as a palliative measure, or as a first stage of complete removal of the cancer. Then at the second operation, complete removal of the bladder and contiguous structures.

This operation may be done in one stage in certain individuals, and I think that it will be the method of choice in the future because if we make a diagnosis of the small tumors early, our experience will eventually teach us that all tumors of the bladder are malignant and we will treat them all radically.

Family Doctor Vaccinating the Baby

(After a sketch by Eytinge. 1878.)

PROVOCATIVE CASE

Carcinoma of the Pancreas

WITH METASTASIS IN THE LUNGS AND SPINAL COLUMN

LEWIS J. MOORMAN AND J. W. MORRISON

OKLAHOMA CITY, OKLAHOMA

THE patient, D. M. H., was a 64-year-old male, employed as a cotton gin operator. His chief complaints were pain in the cervical and upper thoracic regions, radiating to the shoulders and down both arms, with numbness, tingling, and partial loss of function on the right.

He was first seen on February 10, 1948, when he gave a history of progressive loss of strength and endurance for the past three years. In spite of the gradual decline in physical competency he continued his work until November 1947, when he developed an acute febrile attack diagnosed as influenza. Following this acute episode he became physically incapacitated and developed the painful conditions described. The pain progressed in crescendo fashion until he became bedfast. During the long period of physical decline, including the more recent acute developments, there was very little loss of weight. His supine position was maintained chiefly because the slightest movement of his torso or upper extremities caused marked increase in the pain. There was no history of noticeable cough except during the acute respiratory episode.

This patient was referred by Dr. T. H. McCarley of McAlester, Oklahoma, with a suggestion that streptomycin therapy be considered. The following significant statement is taken from Dr. McCarley's letter of June 27, 1948: "You will recall that a number of years ago I referred to you Mr. R. B. H., who had pulmonary tuberculosis. A few weeks ago I was consulted by his son, D. M. H., 64 years of age, who was complaining of severe pain in his chest and shoulders. At that time he had an acute respiratory infection, diagnosed as influenza. After the acute respiratory infection subsided, he continued to have a P.M. temperature of 99.6° F. His blood pressure is 160/100. An x-ray of his chest was made, which I am sending you by this mail. Two sputum examinations were positive for acid-fast bacilli and negative for fungi.

"Of course, I have him at bed rest and his condition is essentially stationary. He still complains of pain in his chest and he lies more comfortably on his back than on either side. I neglected to state in the history that the Mobile X-ray Unit gave him a negative report. This film seems to me to be unusual and suggests miliary tuberculosis."

Past history—A careful survey of past history was unremarkable. Childhood and adolescence were uneventful. He was happily married without issue. Cholelithiasis was once suspected but never proved. A successful herniotomy had been done.

Family history—The patient's mother died of arteriosclerosis. His father suffered from chronic pulmonary tuberculosis in the latter part of his life. This was fairly well controlled by artificial pneumothorax induced after he was past 60 years of age.

Physical examination—General inspection revealed a well developed man of medium stature lying on his back. There was an obvious anxiety complex based chiefly on the fear of movement of his body or even

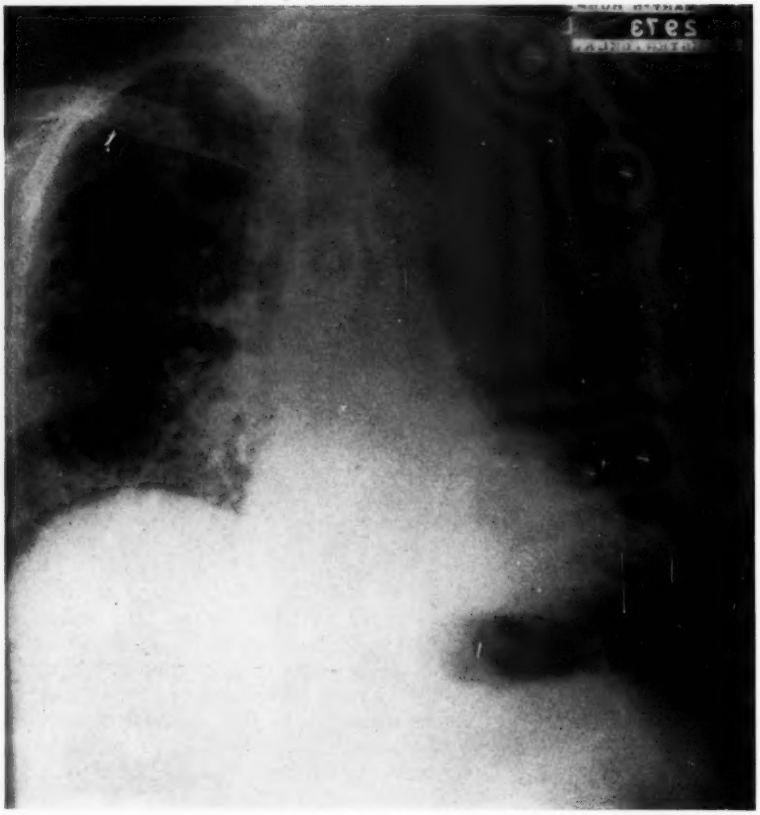


FIGURE 1. Roentgenogram of the chest, made on February 5, 1948, showing widespread miliary densities in both lungs. A film made December 1, 1947, reveals only slight similar nodules in the lower right.

the slightest jarring of the bed. Otherwise the psychologic response was normal. Head, face, neck, nose, throat, and mouth were negative. Physical examination confirmed the paresthesia and loss of function in the upper extremities, suggesting cervical nerve root involvement. Examination of the lungs was considered negative except for fine and medium crackling râles at the base of both lungs posteriorly and rather coarse crackling in the lower left at the anterior axillary line. Examination of the heart revealed a slight mitral murmur which was considered diastolic in time and possibly a slight increase in the area of absolute cardiac dullness. Blood pressure was 140/85, pulse 96. Examination of the abdomen and the genitourinary system gave negative findings. There was a slight angulation of the spine at the level of the fourth thoracic vertebra. Lower extremities were negative.

Laboratory findings reported by Dr. McCarley were essentially negative except for the presence of acid-fast bacilli in two specimens of sputum and certain significant roentgenologic findings. The flat film of the chest revealed what appeared to be widespread bilateral miliary tubercles in both lungs, predominant in the right, with maximum concentration in the middle and lower lung zones on both sides. The heart and great vessels were apparently normal except possibly for a slight increase in transverse diameter of the heart and slight diffuse dilatation of the thoracic aorta. Roentgenograms of the spine revealed moderate scoliosis and slight kyphosis with some evidence of pathology at the level of the fourth thoracic vertebra.

The tentative diagnosis was Pott's disease with secondary or blood stream miliary tuberculosis in the lungs. New growth was considered but temporarily dismissed because of the family history and the two successive reports of acid-fast bacilli in the sputum. The patient was put to bed in the Evergreen Sanatorium. Another sputum smear revealed acid-fast bacilli. Administration of 1½ gm. of streptomycin daily was added to routine sanatorium management.

FIGURE 2. Roentgenogram of the spine on February 5, 1948, showing pathologic changes at the level of the fourth thoracic vertebra and possibly the third. A lateral film afforded no additional pathology.

AFTER a few days there was less complaint of pain, more satisfactory rest with less anodyne and sedative medication. Later there was obvious improvement in the function of hands and arms and much less pain, even when he was raised up in bed for examination. The crackling râles were much less numerous and were heard over a diminishing area. This evidence of continued improvement after a period of three or four weeks caused us to believe that streptomycin was favorably influencing the course of disease in both the spine and the lungs, and gave us an added feeling of security with reference to the diagnosis of tuberculosis. After four weeks of streptomycin the patient requested the privilege of going home to continue the established therapeutic treatment under Dr. McCarley. We still had new growth in mind and deemed it advisable to pursue further the diagnostic study with laboratory facilities not available at the sanatorium. We were particularly interested in roentgenologic studies of the chest and spine for comparison with previous films.

With this in mind it was suggested that before returning home he should be moved to St. An-

FIGURE 3. Roentgenogram of cervical spine, March 16, 1948, showing pathology of fifth and sixth cervical vertebrae. Anteroposterior films did not give any additional information.

thony's Hospital for further laboratory study and consultation. The patient's wife was informed that we had not been able to dismiss the possibility of new growth and that further diagnostic procedures were imperative. This plan was accepted and while roentgenologic studies and other tests were under way he was seen by Dr. Rountree, orthopedist, and Drs. Wilkins and Herrmann, neurosurgeons.

After examination and inspection of films of the spine it was agreed that there was partial destruction of the bodies of the sixth cervical and the fourth thoracic, and also a general demineralization of the bones. Stereoscopic films of the chest indicated that in spite of an obvious diminution in crackling râles there was a marked increase in the density of all previously involved areas and that the nodules previously interpreted as miliary tubercles were larger and individually denser. These films were seen by Dr. Henry C. Sweany of the Chicago Municipal Sanatorium who, in view of the personal and family history and physical and laboratory findings, agreed that according to all indications we were dealing with miliary tuberculosis of the lungs secondary to Pott's disease.

At St. Anthony's Hospital laboratory tests were essentially negative and to our surprise, repeated concentrate sputum examinations for acid-fast bacilli were negative.

Spinal puncture gave a clear, colorless fluid with an original pressure of 110 mm. falling off to 80 mm. with removal of 4 cc. of spinal fluid. Repeated attempts at jugular compression caused no rise in spinal pressure. This was interpreted as indicating a complete subarachnoid space block. Examination of the

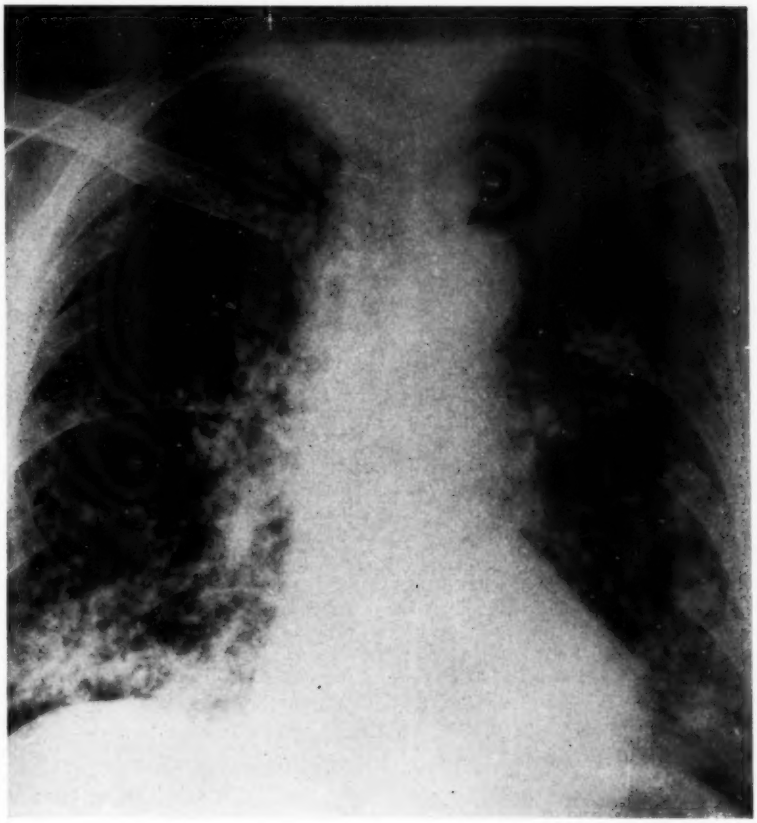


FIGURE 4. Roentgenogram of the chest, March 16, 1948, advancing bilateral pathology in spite of clinical improvement. The annular shadows in the lower left, in location, correspond to the coarse crackling râles elicited upon physical examination.

spinal fluid showed no cells and a total protein of 200 mgm. per cent. Urinalysis (including Bence Jones protein) and complete blood counts were normal. It was still thought that we were dealing with a tuberculous involvement (bones as well as lungs) and head extension was repeatedly attempted but this caused so much pain that it was finally discarded. Drs. Wilkins and Herrmann did not think it advisable to operate at the time. The patient was still receiving 1½ gm. of streptomycin daily.

In view of the fact that no immediate change in treatment was recommended he was dismissed from the hospital April 1, 1948, with instructions to continue his bed rest and streptomycin therapy at home. Soon after returning home in an ambulance his pain became more severe with loss of all function in his legs, and aggravation of the condition in his arms.

He was again hospitalized April 19, 1948. Because he was unable to void, a retention catheter was inserted. There was complete loss of power in the lower extremities with some flatulence and abdominal distress. At no time was there any demonstrable evidence of pathology in the abdomen. The neck pain was partially relieved by acute flexion of the head. On April 22, 1948, a laminectomy (cervical 4, 5, and 6) was done. In spite of the grave prognosis, Drs. Wilkins and Herrmann thought decompression might at least mitigate the pain. They discovered a mass of granulomatous tissue compressing the dural sac and cord. Microscopic examination of this tissue was reported as probably metastatic tumor. The pathologist suggested that we consider hypernephroma as a possible primary source. The patient tolerated the surgery and experienced marked relief from pain but continued on his downhill course. Respiration became more labored and was not aided by oxygen. There was an obvious accumulation of bronchial secretions. The heart action became irregular and supportive measures

were ineffective. On May 4, 1948, he became cyanotic and expired apparently because of respiratory failure.

An autopsy was granted and this abbreviated report includes only the more important findings pertinent to our diagnostic problems. Each pleural sac contained some 300 cc. of clear, straw-colored fluid. The left lung weighed 600 gm. and exhibited innumerable hard, discreet, shot-like masses. These were palpable throughout the lung and on the cut surface were firm and pinkish white. The right lung weighed 900 gm. and was otherwise similar to the left. There were no enlarged mediastinal glands.

The heart weighed 640 gm. and exhibited thickened walls and dilated ventricular cavities suggestive of hypertensive arteriosclerosis. The valves were sclerotic. The great vessels were "atherosclerotic, coronary ostia patent, coronary vessels firm and sclerotic." The aorta exhibited numerous plaques and one small ulcerated area. The liver weighed 2,400 gm., but otherwise was unremarkable. There were several dense adhesions of omentum and bowel in the left upper quadrant, about the tail of the pancreas. The pancreas weighed 200 gm. and there was a stony, hard mass occupying the entire tail which cut with marked resistance and on cut surface appeared pearly white, homogeneous, and cartilaginous-like. This did not invade the surrounding tissue and no involved lymph nodes were found. Microscopic examination of the nodules in the lungs and pancreas showed the tumor masses to be "scirrhous adenocarcinoma, probably primary of the pancreas."

This case presented a number of puzzling questions and to our chagrin some of them remain unanswered. Though forewarned by knowledge and experience, we rested too implicitly upon the diagnosis of tuberculosis as the explanation of both the pulmonary and the spinal pathology. While it was easy to accept the comfortable impression that all the abnormal manifestations might reasonably be attributed to the well known tricks of the tubercle bacillus, we subconsciously kept our fingers crossed with new growth in mind. Yet it seemed reasonable to attribute the three years of physical decline to the atypical manifestations of tuberculosis so common in elderly people. It was equally easy to believe that the acute respiratory episode in November, 1947, fanned a smoldering fire into flame, especially when three sputum smears revealed acid-fast bacilli.

Under the influence of this diagnostic buildup we were not sufficiently alerted by the fact that Pott's disease seldom presents multiple foci; likewise we were diverted from the advisability of proving the specificity of the acid-fast bacilli by culture or animal inoculation and we neglected to employ the tuberculin test. Also the pathologist seemed to overlook the fact that we had made a clinical diagnosis of pulmonary tuberculosis. Consequently the tissue specimens were taken only from the areas of the lungs most densely studded with the small tumorous nodules and the microscopic studies admittedly followed the same pattern. When the first draft of the autopsy report failed to show any detailed study of the lung tissue except for tumor, the pathologist was requested to make a study for evidence of tuberculosis. Having only the specimens mentioned above, he gave the following supplementary report:

"Lungs: Slight anthracosis and tumor invasions. Alveoli are both filled with and replaced by the tumor which is definitely glandular and similar to that described elsewhere.

"Sections showing tumor show no evidence of tuberculosis—very little lung tissue remaining.

"Tissue is so invaded by tumor that we made no special sections for areas of tuberculosis, but in the sections we did make, we found no evidence of tuberculosis."

In view of all the evidence and keeping in mind the occasional phenomenal therapeutic action of streptomycin, and allowing for the imperfect pathologic search for pulmonary tuberculosis gross and microscopic, we believe that in this case we were dealing with pulmonary tuberculosis associated with primary adenocarcinoma of the tail of the pancreas, metastatic in the spine with widespread seeding in both lungs—also hypertensive arteriosclerosis.

Scientific Exhibit

Orthostatic Hypotension and Orthostatic Tachycardia

ANTON S. YUSKIS, M.D. and GEORGE C. GRIFFITH, M.D.

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The syndrome of orthostatic hypotension and orthostatic tachycardia results from an inadequate return of venous blood to the heart. The essential factor is a generalized abnormally low capillary venous tone.

The postural hemodynamics in the normal adult and those in the syndrome of orthostatic hypotension are shown in the illustrations.

In postural hypotension, as the erect position is assumed, blood pools in the lower part of the body and a sharp fall in blood pressure with weakness, faintness, or syncope occurs. This reaction to the upright posture is usually most severe in the morning.

The hemodynamics of this syndrome are shown by the changes that take place in the retinal vessels with the changes of posture. With the patient supine, elevation of the legs produces retinal hyperemia, distention, and tortuosity of the vessels, particularly the veins, slight increase in blood pressure, somewhat slower pulse rate, and a shorter circulation time. When the legs are lowered, the retinal vessels contract and the retina becomes less hyperemic.

Upright position brings the circulatory defect into full play, causing extreme pallor of the optic disk and fundus, contraction of the retinal vessels, a drop in blood pressure, accelerated pulse rate, rise in venous pressure and a prolonged circulation time. These changes are reversed when the patient assumes the supine position.

The blood pressure is normal in the supine position but in the erect position the blood pressure may fall below 50-60 mm. mercury systolic, especially early in the morning or after exertion.

Orthostatic hypotension should be suspected if exhaustion is present in the morning but decreases during the day, if dimness of vision, faintness, and unexplained syncope are produced by standing and abolished by lying down.

The electrocardiographic tracings may show abnormal rhythm and/or S-T-T complexes with a change in posture. In the illustration, when the patient stood up, normal sinus rhythm was replaced by premature contractions of auricular and ventricular origin followed by auricular fibrillation. Sinus rhythm was restored by lying down and raising the legs. The mechanism responsible for these changes is due to the decreased venous return to the heart and the resulting myocardial anoxia.

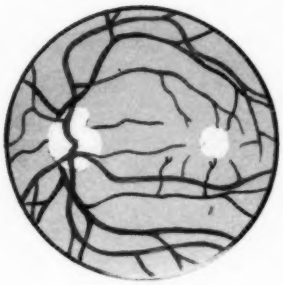
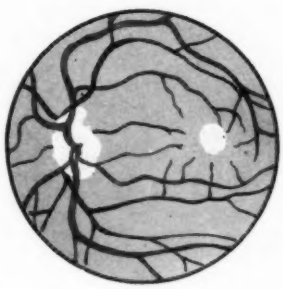
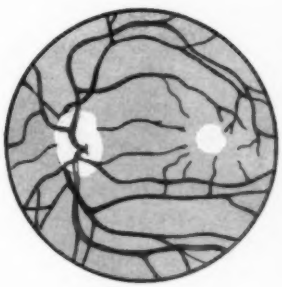
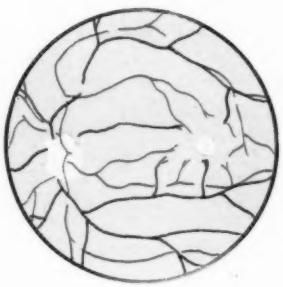
Symptoms of orthostatic hypotension were satisfactorily controlled by a single large daily dose of paredrine hydrobromide; 100-200 mg. were taken orally thirty to sixty minutes before rising. The treatment is symptomatic and no claim to a cure is made.

The mechanism responsible for the maintenance of normal capillary venous tone is not fully understood. Because of the absence of this tone, a sympathomimetic drug, without any central action, relatively nontoxic, and safe in large doses orally, was used. It was given at a time when it was most needed so that by its vasopressor effect the capillary venous tone would be increased, resulting in an increased venous return to the heart.

VASCULAR RESPONSES IN ORTHOSTATIC HYPOTENSION

Position of patient	*Blood pressure mm. Hg.*	*Pulse per minute*	*Venous pressure mm. of water*	*Circulation time arm-tongue-seconds*
Supine	105/74	84	0° — 65 mm.	18
Supine Legs elevated	120/80	80		12
Supine 30° angle	90/50	94	45° — 78 mm.	20
Standing	1 min. 88/68 2 min. 30/0 3 min. 0/0	96 110 120 (?)	90° — 88 mm.	26

VASCULAR RESPONSES IN ORTHOSTATIC HYPOTENSION

Retinal Vascular Pattern **Before Treatment**		*Retinal Vascular Pattern* **After Treatment**	
Both pattern and color are normal		No significant change in either pattern or color	
Increased redness of the disk and the fundus. Marked distention of the veins and arterioles and marked tortuosity of the veins		Lessened redness of the disk and the fundus. Slight to moderate distention and lessened tortuosity of the veins. No apparent change in arterioles	
Slight pallor of the disk and of the fundus. Slightly smaller veins		No significant change in either pattern or color	
Marked pallor of the disk and of the fundus. Veins empty before the arterioles. Both veins and arterioles are narrow and only faintly visible.		Slight pallor of the disk and the fundus. Veins and arterioles are well filled and are clearly visible.	

(Veins are shown in red; arteries in black)

VASCULAR POSTURAL RESPONSES IN NORMAL ADULT

Position of patient	*Blood pressure*	*Pulse*	*Retinal vascular pattern*
Supine	120/80	72	Normal
Vertical Head down	128/84 1 min.	77	No significant change from normal
Supine Legs elevated	128/84	74	No significant change from normal
Standing	At start 124/88 3 minutes 122/80	At start 82 1 min. 80 2 min. 75 3 min. 74	No significant change from normal

CARDIAC ARRHYTHMIA OBSERVED IN ORTHOSTATIC HYPOTENSION

Position of patient

Supine

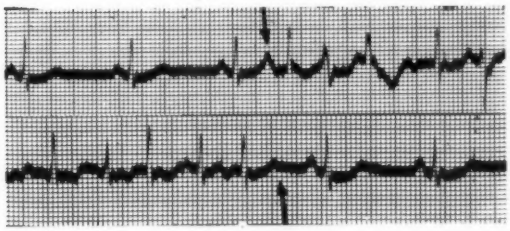
Standing

Electrocardiogram

Normal

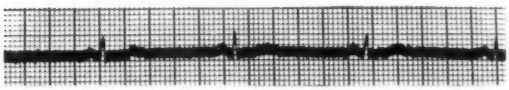
Before treatment *Abnormal rhythm*

Onset



Offset

After treatment *Normal rhythm*



EFFECT OF TREATMENT WITH PAREDRINE HYDROBROMIDE

Subjectively
Relief of symptoms

Objectively
Increased venous return to heart

Method of Administration
Time: 30-60 minutes before getting out of bed
Dose: One or single dose—up to 200 mg.
Route: Oral
Side Effects: None

SUMMARY

1. *Site of disorder*
   a. Abnormal capillary venous tone
2. *Clinical evidence to support this view*
   a. Changes in retinal vascular pattern
   b. Changes in blood pressure
   c. Circulation time prolonged
   d. Changes in venous pressure
   e. Cardiac arrhythmia

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GENERAL PRACTICE *Review*

To provide the general practitioner, as well as the specialist with concise, readily available information on the latest, proved methods of treatment of conditions commonly encountered in an average practice, POSTGRADUATE MEDICINE *offers this department to its readers. It is not, of course, intended to present these discussions as the only acceptable therapeutic procedures to be used, but rather to offer simple regimens and recommendations based on the extensive experience of the physicians who prepared these summaries.*

Treatment of Rosacea

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THE clinical entity known as rosacea may be due to any one or a combination of several causes; hence the treatment may vary considerably depending upon the etiology.

Although most texts do not stress the fact, I am convinced as the result of many years of observation that there are at least two principal types of rosacea, one of external origin and one of internal origin. Success or failure in treatment may depend upon a recognition of these two types.

The "external" type of rosacea is caused by an infestation of the small animal parasite known as Demodex folliculorum, an organism normally present in small numbers in the sebaceous ducts, especially of the face, in practically all adult humans. These mites which belong to the spider family usually occur in relatively small numbers and apparently live on the sebaceous secretion in a saprophytic capacity and because they do not burrow into the skin they cause no symptoms. Occasionally, however, they become numerous, usually as the result of the use of excessive facial make-up and inadequate cleansing ("cleansing cream" instead of soap and water) and under these circumstances they may set up an inflammatory reaction resulting in a diffuse flushing of the face, not necessarily restricted to the front of the face, accompanied by a burning or itching sensation.

Close inspection reveals a dry, rough, nutmeg-grater like appearance which is quite distinct on palpation and is made up of tiny white follicular plugs or scales. There are usually a few superficial vesico-pustules. These patients are usually women but men may be affected and in 2 patients seen the process also involved the bald area on top of the scalp.

The diagnosis of demodex infestation can readily be made by microscopic examination of fluid from vesico-pustules or tiny follicular scales which have been picked off with a fine-pointed forceps. The material is examined under the low power after adding a drop or two of 40 per cent potassium hydroxide and covering with a cover slip. The preparation should not be heated but should stand for five to ten minutes. Sometimes enormous numbers of these mites can be seen and it is not uncommon to count ten to fifteen in a single low power field. This is in striking contrast to the absence or relatively infrequent occurrence of these parasites in pus from other types of rosacea or from acne vulgaris.

It is impossible to eradicate these mites completely but their numbers can be reduced appreciably and concomitant eruption relieved, sometimes in a dramatic fashion, by the use of a suitable parasiticide such as a compound sulfur ointment (Dan-

ish Ointment) which is to be applied to the face for three consecutive nights after first washing with soap and water. Care should be taken to avoid getting the ointment in the eyes and onto the tender part of the neck. Occasionally local irritation prevents its being used for more than one or two nights but usually the ointment is tolerated remarkably well.

The ointment should be washed off in the morning and a mild cold cream may be applied if there is irritation. The face should be washed gently with soap and water at least once daily as a permanent routine. Subsequent applications of the ointment will depend upon the symptomatic response and the demodex count. It is usually necessary to continue the ointment with diminishing frequency, such as once or twice weekly, over a period of a month or two. For this type of rosacea no amount of dieting or internal medication will be of any value.

The "internal" types of rosacea usually lack the dry, nutmeg-grater appearance and in fact often have a tendency to seborrhea and the eruption is usually confined to the front of the face. Here again, a diversity of underlying causes may be involved including menopausal changes, vitamin B deficiency, anemia, gastrointestinal disturbances, psychosomatic complexes, focal infection, etc., and intelligent treatment must take into account the possibility of these various factors.

Dilute hydrochloric acid when a deficiency exists, high potency vitamin B complex and iron when indicated, crude liver extract containing folic acid by intragluteal injection, etc., are some of the more valuable internal types of medication. A bland diet with avoidance of foods likely to cause gastric distress as well as excessively hot or cold drinks should be followed.

Local therapy will vary according to circumstances. If there is a good deal of seborrhea, fractional superficial roentgen therapy administered by a physician *qualified* in such procedures may be useful. Neocalamine lotion (N.F.) during the day and Lotio Alba at night are often valuable.

Lotio Alba:

℞ { Zinc sulfate 10-15
Rose water 60
Potassium sulfurette 10-15
Rose water 60

Undue exposure to the sun or heat and the internal use of alcohol should be avoided in all types of rosacea inasmuch as they tend to cause an increased flushing of the skin and an aggravation of the symptoms.

Management of Cases with Meningeal Signs

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In the general practice of medicine, two cardinal errors are all too frequently made in dealing with the patient who shows signs of meningeal irritation. The first, obviously, is to overlook these signs until valuable time has elapsed. The second is to start treatment in a flurry of excitement without reasonably clear thinking as to etiologic diagnosis, and without having undertaken necessary laboratory procedures to establish such a diagnosis.

The florid picture of meningitis is impossible to mistake. A patient with bursting headache, fever, vomiting, delirium, and rigid spasm of the extensor muscles of the neck instantly stimulates medical thinking along appropriate lines. It is not so in the case where these manifestations are more subtle. The *early* diagnosis of bacterial meningitis is frequently delayed because the practitioner doesn't happen to think of it, and this is even more true of nonbacterial varieties.

In order to avoid this error it is worth reemphasizing certain simple principles. Most acute febrile illnesses are presumed to be due to common respiratory infection. Severe and persistent headache is *not* a feature of common respiratory disease—it should suggest meningeal irritation (as well as other things, such as infectious mononucleosis and rickettsial infection). Neither are repeated vomiting or marked lethargy. Moreover, with the exception of bacterial pneumonia and streptococcus pharyngitis, ordinary respiratory in-

fection does not produce leukocytosis. Any of these findings should make the practitioner doubly alert in his search for meningitic signs. **The cardinal sign,** of course, **is stiffness of the neck,** which, even if present in only slight degree, must be considered significant.

The treatment of bacterial meningitis is different from the treatment of nonbacterial varieties; moreover, the treatment of the various types of bacterial meningitis is not the same. Hence the paramount importance of precise etiologic diagnosis wherever this is humanly possible. Now if antibiotics or chemotherapy has been instituted before spinal fluid, blood, etc., have been obtained for culture, negative findings lose their significance, and the practitioner may find himself confronted with a continuing situation wherein he must order appropriate therapy for a disease the nature of which is obscure. Thus it follows that the habitual use of small doses of these drugs in minor acute illness will very successfully obscure the diagnosis if meningitis is, in fact, developing.

It is of the utmost importance, therefore, to defer treatment of any case of suspected meningitis until suitable samples of spinal fluid and blood have been obtained and sent to a good laboratory for bacteriologic and other studies.

Generally speaking, spinal fluids divide themselves at the bedside into those which are grossly turbid and those which are clear, or only slightly hazy. Fluids of the former category are an indication for immediate specific treatment, as they point to bacterial meningitis. These turbid fluids are characterized by a preponderance of polymorphonuclear leukocytes and a marked reduction in the sugar content.

Not all bacterial agents, to be sure, produce turbid fluids with polymorphonuclear pleocytosis: the tubercle bacillus does not, nor does cryptococcus hominis. They produce low total counts with a preponderance of lymphocytes, but they also result in lowering of the spinal fluid sugar. Immediate treatment is not indicated in these conditions until a positive diagnosis is made. It follows, therefore, that immediate treatment is warranted in all cases where the fluid is grossly turbid, and should be withheld initially in almost all cases where it is clear or only slightly hazy. An exception in the case of the clear or slightly hazy fluid should be made if microscopic examination shows the cell type to be polymorphonuclear. Occasionally very early bacterial meningitis may present itself thus, and it is probably safer to treat all "polymorphonuclear fluids."

Meningitic signs may be caused by infection with nonbacterial agents. These include such recognized viruses as those of lymphocytic choriomeningitis, equine encephalomyelitis, St. Louis and other encephalitides, poliomyelitis, mumps, and probably some unidentified viruses. They may also occur in infectious mononucleosis, and as a late complication of vaccinia and some of the exanthemata, where the lesion is believed to be a demyelinating one. The spinal fluids in these conditions are all essentially similar; they have low cell counts, usually in the 50 to 200 range, almost always under 1,000, with great predominance of lymphocytes, and a normal sugar content. (A very rare exception to the lymphocytosis must be noted: occasionally in early poliomyelitis and in one or two outbreaks of aseptic meningitis, transitory polymorphonuclear preponderance has been described, but the total counts are low, and the sugar normal.) This same type of fluid as that seen in nonbacterial meningitis is also found in "méningite de voisinage"—i.e., meningeal irritation associated with an adjacent focus of infection. Broadly speaking, where fluids of this character are obtained, no specific treatment is indicated, but every effort at etiologic diagnosis should be made.

To return to the management of the patient with grossly turbid fluid: If a rash is also present, the diagnosis of meningococcus meningitis may be confidently assumed. This does not obviate the necessity for blood and spinal fluid cultures, but it does influence immediate therapy.

And now let us make a statement, of the truth of which I am convinced: **Sulfadiazine** is still the principal agent of choice in the treatment of meningococcus meningitis, and it is an important adjunct to the treatment of all forms of purulent meningitis except those due to an organism proved to be insusceptible to its action. It penetrates well into the subarachnoid space, it does not require repeated lumbar taps for administration, and extremely good results were obtained with it in cerebrospinal fever before the introduction of penicillin. Thus in a case of meningococcus meningitis of average severity I see no reason to employ intrathecal penicillin. It is our custom to give an adult 5.0 gm. of sodium sulfadiazine in a liter of saline by vein, followed, perhaps, by 500 to 1,000 cc. of 1/6 molar lactate.

The object of sulfadiazine therapy is to establish and maintain a blood level in the range of 12 to 15 mg. per cent, and it is of obvious importance to estimate the blood level six or eight hours after this initial dose. If the patient can take medication by mouth, sulfadiazine may be started about this time in doses of 1.0 to 1.5 gm. every four hours, depending on blood levels. Naturally the hazards of sulfadiazine therapy must be borne in mind, and full attention to fluid intake and

output, blood counts, etc., must be maintained.

It will be noted that no mention has been made of intramuscular penicillin for the reason that while I consider it a very valuable adjuvant to the treatment of cerebrospinal fever, I still regard it as secondary to sulfadiazine. There is absolutely no contraindication to its use, however, in cases of mild to moderate severity, and it is our custom to employ it during the first days of the disease. In very severe cases, in those which have been of some duration before treatment is begun, and particularly in the so-called "Waterhouse-Friderichsen syndrome," it should be used to the utmost—intrathecally (in amounts not exceeding 25,000 units), and in large doses at three-hour intervals intramuscularly.

Generally speaking we maintain sulfadiazine treatment for at least a week in mild to moderate cases, and somewhat longer in the severe ones. Lumbar punctures (apart from the initial diagnostic tap) are not part of the routine treatment. They are employed for the relief of symptoms if necessary, in order to appraise the progress of the case if there is any reason to think it unsatisfactory, and for intrathecal treatment where indicated.

Purulent meningitis *without* a rash may or may not be due to the meningococcus. In infants and small children it may be caused by H. influenzae. At any age it may be pneumococcal or streptococcal. An antecedent history of mastoiditis, sinusitis, head injury, etc., are points in favor of the last-named. Where one is dealing with these two Gram-positive pyogens, it must be remembered that the resulting meningitis is a much more serious affair than that due to the meningococcus. Treatment, therefore, should be correspondingly more intensive, i.e., full doses of sulfadiazine, penicillin intrathecally at least once a day for the first few days, and large doses of penicillin (say 500,000 units) every three hours intramuscularly. It is also our custom, based on experience with relapses, to maintain treatment longer—in the pneumococcal cases, particularly, for at least three weeks. Moreover, an exhaustive search for treatable foci of infection must be made from the very beginning.

The agents of choice in H. influenzae meningitis are sulfadiazine and streptomycin used in combination. It must be reemphasized that the right agents cannot be employed in the absence of exact bacteriologic diagnosis. An additional weapon in this disease is H. influenzae Type b concentrated rabbit antibody solution, given intravenously in very severe cases in addition to the other treatment.

Purulent meningitides due to pyogenic organisms other than the above are comparatively rare. Such cases pose a difficult problem in therapy, wherein one must make the utmost use of expert bacteriologic assistance. Sensitivity tests must be performed, and the appropriate antibiotic and chemotherapy applied to a maximal degree.

Treatment of Congestive Heart Failure

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The diagnosis of congestive heart failure having been established, it is imperative to institute a plan of treatment whereby the patient can be quickly returned to a state of normalcy.

In the past there has been a more or less hopeless attitude of digitalization, rest in bed, and watchful waiting. With the newer concepts of the role that sodium plays in the retention of fluid, a new approach to treatment is open. **Digitalis and rest** are still essential in their part of the program. The type of rest depends on that most comfortable to the patient and the preparation of digitalis should be that with which the physician is most familiar. Mercurial diuretics have been found to be of inestimable value in the therapeutic program.

Rest—Rest should be both physical and mental. Allow the patient to finish as much business as possible before he is confined to bed. If the patient is more comfortable in a chair there is no reason one can't be used. Dependent portions of the body are likely to become "water logged"; rest in bed is therefore more frequently used. The patient should be cautioned regarding change of position at hourly intervals with periods of deep breathing and exercises to promote return flow of blood from the extremities. Small doses of barbiturates are of great value and induce sleep, so essential to the patient. Visitors should be limited.

Digitalis—Although digitalis has been used for about two centuries, only in recent years has the extreme variation in dosage required by different patients been thoroughly understood. A set dosage or one governed by body weight will not always suffice. In patients who have fibrillation, the dosage can be more easily judged, knowing that a reduction of pulse rate to between 70 and 90 beats per minute is about the optimum in response. In patients without fibrillation, the exact dosage is more difficult to ascertain and should be judged by clinical improvement. The digitalizing dose per patient may vary from 5 to 40 cat units and the maintenance dose from 2 cat units weekly to 2 cat units daily. When rapid digitalization is desired the intravenous route is used.

The preparations most frequently utilized are digitoxin 1 mg., Cedilanid 1.6 mg., ouabain 0.4 mg, or 3 U.S.P. units of any injectable digitalis. In the majority of cases the oral route suffices and one of the more rapidly absorbed and quickly utilized preparations is Digitaline Nativelle. The average digitalizing dose of 1.2 mg. can be given at one time and is usually adequate. This preparation—1,000 times as strong as digitalis leaf, and a pure glycoside—can be given in one dose without, as a rule, precipitating toxic symptoms. The therapeutically equivalent dose of the leaf (1.2 gm.) or the tincture (12 cc.) usually causes gastric irritation. If 1.2 mg. of digitoxin is not adequate, small supplemental doses may be given until digitalization is obtained. The maintenance dose is ordinarily 0.2 mg. daily, but this can and does vary.

Diuretics—The diuretic can be varied among many drugs. Orally, the xanthines, urea, and ammonium chloride are available, but in the majority of patients an effective dose is not tolerable due to the side effects of gastrointestinal distress, drowsiness, diarrhea, cerebral stimulation, or even alarming states of acidosis.

The most effective diuretics now in use are the **mercurials.** Deaths have been recorded from their use as diuretics but these have all been the result of intravenous injection. The three mercurials used are Mercuhydrin, Salyrgan-theophylline and Mercuzanthin, which are generally given intramuscularly. If sensitivity to a specific mercurial develops it may become necessary to use one of the others. Mercuhydrin causes less localized reaction in the muscle.

When the mercurial diuretics are to be used, the patient is weighed and the original dose of 0.5 cc. is given intramuscularly. If there is a definite weight loss with this dose it is repeated daily. If no weight loss is observed the dose is increased to 1 cc. or 2 cc. daily or every other day, depending on the weight loss. A desirable weight loss is 4 pounds daily, which is continually strived for until the patient reaches a so-called "dry weight." If weight is lost too rapidly, weakness or muscle cramps may develop. These symptoms are the result of salt loss and may be promptly cured by very small doses of sodium chloride.

Patients ordinarily receive mercurial diuretics at too infrequent intervals and may develop symptoms of congestive failure if the dose is long delayed. It is our practice to give smaller and more frequent doses. The principal factor that governs the dose and its frequency is the weight of the patient.

Renal damage has been reported following the use of mercurials. There are also numerous reports of long continued use of the drug without harm. Though there may appear signs of renal damage, there is evidence that it is reversible, after the drug has been discontinued. Urinary analyses and nonprotein nitrogen determinations lead one to suspect impending damage, at which time the mercurial in use can be omitted for a few days and then readministered.

Diet—In obese patients reduction is absolutely indicated and in all patients, the sodium ion intake and protein needs must be carefully observed. Gas-forming foods should be avoided. The importance of watching the sodium ion intake cannot be overemphasized. Frequently the physician orders a salt free diet only to find the patient receiving saline laxatives or food unseasoned with salt but with salt shakers on the tray. All foods cooked with baking powder or baking soda are eliminated, as are foods high in sodium content.

Foods may be seasoned with lemon juice, herbs, vinegar, pepper, and unsalted butter. Most canned and fresh fruits are permissible as are practically all vegetables. Drugs such as sodium salicylate, sodium bromide, and others containing the sodium ion are to be used sparingly. The protein intake of the patient should be 1 gm. per kilogram of body weight.

SUMMARY

The treatment of congestive heart failure involves four principal approaches. These are adequate rest, the intelligent use of digitalis or one of the glycosides, a drastic reduction in the intake of the sodium ion, and the long continued use of one of the mercurial diuretics.

The Medical Bookman

► THE EPITOME OF ANDREAS VESALIUS - - -

Translated from the Latin by L. R. Lind, Ph.D.; Anatomical Notes by C. W. Asling, M.D. Publication No. 22, Historical Library, Yale Medical Library. 107 pages. 1949, The Macmillan Company, New York. $7.50.

Vesalius' great classic *De Humani Corporis Fabrica* is a bulky work, and difficult to read. As if aware of this handicap, the father of modern anatomy and also of medicine, wrote a brief condensation of it, entitled "The Epitome," and published it at Basel in 1543, the same year that saw the publication of the "De Revolutionibus," the famous classic of Copernicus.

The Epitome, here for the first time rendered into English, is a lucid synopsis of the greater work, more pleasant to read and conveying the master's skill in anatomic studies, his facile though pedagogical style, as well as the orderly development of his new outlook and meticulous detail, with even greater effect than the Fabrica.

No student of medicine cognizant of the cultural and educational value of the historical background can afford to miss this previous insight into the pioneering quest for a science of anatomy. The translation is excellent and the notes and chapter summaries most helpful. The reproduced plates from the original edition are a bonus and possess unique charm and merit.

M. G.

► BLAKISTON'S NEW GOULD MEDICAL DICTIONARY - - -

Edited by Harold Wellington Jones, M.D., Colonel, U.S. Army, Retired, Former Director, Army Medical Library, Washington, D.C.; Normand L. Hoerr, M.D., Ph.D., Professor of Anatomy, School of Medicine, Western Reserve University; Arthur Osol, Ph.D., Professor of Chemistry, Director of Chemistry Departments, Philadelphia College of Pharmacy and Science, Editor-in-Chief, United States Dispensatory. With the assistance of an editorial board and over 100 contributors. 1294 pages, 252 illustrations, 129 in color. The Blakiston Company, Philadelphia, 1949. $8.50—textbook edition; $10.75—thin paper edition; $13.50—deluxe edition.

Described as the "first new medical dictionary in thirty-eight years," this work is the result of painstaking effort on the part of specialists in all branches of medicine and the allied sciences, and an expert editorial staff. The project was initiated by Dr. Harold W. Jones in 1944 while he was still director of the Army Medical Library and he arranged for the use of the facilities of the Cleveland Branch of the Army Medical Library. The editors have included a vast number of new words which have come into medical usage in recent years, and have simultaneously removed thousands of words now obsolete. A new series of anatomic drawings were prepared for the dictionary, many of them in color and all drawings, photographs, and tables are cross referenced with the text.

A. E.

► THE MANAGEMENT OF BINOCULAR IMBALANCE - - -

By Emanuel Krimsky, M.D., Adjunct Professor of Ophthalmology, New York Polyclinic Medical School, Assistant Attending Ophthalmologist, New York Polyclinic Hospital, Lieutenant Colonel, Medical Corps Reserve, U. S. Army. 464 pages, with 200 illustrations. 1949, Lea & Febiger, Philadelphia. $12.50.

Dr. Krimsky's worthy contribution joins a small group of books concerning extraocular motor anomalies which have been published in recent years. The author devotes a chapter to a careful description of his corneal light reflex test and shows that it is an excellent addition to the armamentarium of objective testing of binocular balance and imbalance.

The rest of the book describes the motor phenomena based on measurement of the light reflex, rather than of the eye movements, the usual objective method. For one accustomed to measuring ocular movement, use of the light reflex method might be confusing at first; nevertheless, it could be a valuable adjunct. The explanatory drawings on action of muscles are good.

Krimsky discusses at length his prism reflex test and anglometer for measuring the anomalies. The author emphasizes the point that heterophoria is frequently compatible with normal binocular balance and only when it is studied with regards to prism vergence can its true significance in a specific case be evaluated. He feels that in vertical anomalies the terms "right and left hypertropia" should be replaced by "hypotropia" when it helps point out which eye is the defective one.

The experienced ophthalmologist will find this book valuable as a review of extraocular motor anomalies from a different point of view.

H. S. F.

► PATHOLOGY AND SURGERY OF THYROID DISEASE - - -

By Joseph L. DeCourcy, M.D., Senior Surgeon, Good Samaritan Hospital; Director, DeCourcy Clinic, and Cornelius B. DeCourcy, M.D., DeCourcy Clinic Surgical Staff, Cincinnati, Ohio. 476 pages, illustrated. 1949, Charles C Thomas, Springfield, Illinois. $10.00.

This treatise is based on the authors' personal experience with over 15,000 cases of thyroid disease, including hypo- and hyperfunctioning of the thyroid. An excellent review of embryology, anatomy, histology, physiology, pharmacology, and pathology in reference to the thyroid is presented. The text describes in detail preoperative care, type of anesthesia used, and operative technic, and discusses the development, use, and present status of radioactive iodine as well as the use of antithyroid drugs.

The authors discuss Riedel's struma at length, their theory being that the basis of this condition is a perithyroiditis which is primarily responsible for the woody consistency of the gland. In their series, not a single case occurred in association with a pre-existing goiter.

N. B.

► ESSENTIALS OF ORTHOPAEDICS - - -

By Philip Wiles, M.S., F.R.C.S., F.A.C.S., Secretary, British Orthopaedic Association; Treasurer, Editorial Board, Journal of Bone and Joint Surgery. *486 pages, 7 color plates, and 365 text figures. 1949, The Blakiston Company, Philadelphia and Toronto. $10.00.*

This book is written by an English surgeon who felt the need of a textbook on orthopedics for the general practitioner, student, and the beginner in postgraduate surgical training. For this reason he has placed emphasis on those phases which are of more interest to this group and treatment is described in detail when it can be carried out by a general practitioner.

The problem of back pain, known to everyone who practices medicine, is handled very well by the author and is an example of how other problems are presented.

The author divides back pain into four main groups: acute and chronic back pain, coccydynia, and back pain associated with sciatica. A full history is said to be very important and mistakes in diagnosis made less likely if a full routine is always followed. The scheme of examination is outlined and each maneuver well illustrated. In acute back pain he states that in many instances the etiology is quite unknown, the only cause known definitely being protusion of intervertebral disk.

Chronic backache is said to offer even more difficulty in diagnosis. Here again the author treats the subject realistically. While realizing that in many instances no cause can be found, he shows how it is advantageous to have in mind a classification of the more usual causes of chronic back pain even though it is not always possible to be precise as to etiology in a particular patient.

Y. S.

► NEUROLOGY - - -

By Roy R. Grinker, M.D., Director, Institute for Psychosomatic and Psychiatric Research and Training and Chairman, Department of Neuropsychiatry, Michael Reese Hospital, Chicago; and Paul C. Bucy, M.D., Professor of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago. Ed. 4. 1,138 pages, illustrated. 1949, Charles C Thomas, Springfield, Illinois. $12.50.

Since the first edition of *Neurology* appeared, Dr. Grinker has shifted much of his interests to the fields of dynamic psychology and psychiatry. Thus, it was natural that he invite his former colleague Dr. Paul C. Bucy to collaborate in revising this book.

The change in authorship as well as passing time have resulted in many alterations but the book remains a presentation of neurology on a broad, general basis. The section on electroencephalography has been rewritten with the cooperation of Dr. F. A. Gibbs. New changes in therapy with the sulfonamides, penicillin, and streptomycin have been introduced.

Disproved observations and hypotheses are removed and the first four chapters omitted from this edition as entities. Much of the material they contained has been written into the remainder of the text and integrated more closely with the clinical material. The authors have aptly correlated neurologic disease with the structure and function of the nervous system.

Bibliographic data have been assembled at the end of the book, making readily available reference to excellent monographs on other details of neuroanatomy, neurophysiology, and neuropathology not included here.

R. M.

► STOMACH DISEASE AS DIAGNOSED BY GASTROSCOPY - - -

By Eddy D. Palmer, A.B., M.S., M.D., Major, Medical Corps, U. S. Army. Formerly Chief, Gastrointestinal Section, Walter Reed General Hospital, Washington, D.C. 200 pages, with 53 illustrations and 56 plates in color. 1949, Lea & Febiger, Philadelphia. $8.50.

In the preface the author describes this text as a point of departure for the physician who is already familiar with the contraindications, technic, and orientation of gastroscopy.

The first chapter discusses the gastroscopic picture of the normal stomach, while subsequent chapters deal with such conditions as anomalies, mucosal vascular diseases, ulcers and erosions, the gastritides, granulomas, adenomas, carcinomas, and sarcomas. There is also a chapter on gastroscopic view of the postoperative stomach and gastroscopy in certain metabolic and skin diseases. The last chapter is a very instructive one on the subject of errors in gastroscopic diagnosis.

One of the most common reasons for a patient to be gastroscoped is to rule out the presence of a malignancy. The author states that the need for a precise anatomic diagnosis in cancer is ever present and that gastroscopy can give it. He says that diagnostic potentialities of gastroscopic method in cancer are tremendous and that endoscopy can establish a diagnosis when other diagnostic methods fail to indicate disease. He firmly believes that the routine use of gastroscopy will result in better control of gastric cancer.

Y. S.

► PSYCHOSOMATIC MEDICINE; The Clinical Application of Psychopathology to General Medical Problems - - -

By Edward Weiss, M.D., Professor of Clinical Medicine, and O. Spurgeon English, M.D., Professor of Psychiatry, Temple University Medical School, Philadelphia. Ed. 2. 803 pages. 1949, W. B. Saunders Company, Philadelphia and London. $9.50.

The appearance of a second edition of this well received and well written book is of importance after an interval of six years since the first edition appeared early in the war. Now the authors have utilized much of the interesting and valuable material which came to light in the armed forces.

Commonly both publishers and authors direct texts of this general nature to both the lay and the medical readers because of the widespread public interest. Almost invariably such books serve neither purpose—the education of the doctor nor the public. But here is an unusually well written book definitely directed to the practitioner of medicine geared to practical use and highlighted by the use of italics and blocked key points. It is well organized. The bibliography, index, and appendix are interesting and useful. The publishers have produced an attractive and sturdy book.

The new edition has been rearranged so that material of a general nature makes up Part I, with the applications to special problems in Part II. Much has been rewritten and considerable new clinical material has been added. In particular, there is a new chapter on psychosomatic diagnosis which includes advances in psychologic testing that have been applied to psychosomatic diagnosis and prognosis. Material on social work in relation to psychosomatic medicine; on orthopedic and physical medicine have been added. New charts, tables, and treatment suggestions are included.

H. W.

► ATLAS OF ROENTGENOGRAPHIC POSITIONS - - -

By Vinita Merrill, while Educational Director, Picker X-ray Corporation. In two volumes. 663 pages, illustrated. 1949, C. V. Mosby Company, St. Louis, Missouri. $30.00.

The relative positions of the body, the focal spot of an x-ray tube and a film, by which a clear, undistorted image of a particular organ or structure is assured, may and have been established. Procedures applicable to all parts of the body have been published, at one time or another, in many languages and many journals. Instructions for body-part positioning have been included in manuals of roentgenographic technic.

Vinita Merrill has selected from original sources in English, German, French, Swedish, Spanish, Italian, and other native literature descriptions of all standard methods, and of those occasionally required in unusual circumstances. References to articles used, general texts and journals in which new ideas are likely to appear, are listed. A complex index for both volumes is printed in each. The end papers, with portraits of the scientists who contributed to the development of roentgenography, are interesting.

Anatomic information necessary for understanding the position, shape, and location of an organ to be visualized, relation to adjacent structures or parts intervening between tube target and film, is adequate. The general rule adopted is adjustment of tube, body and film so that the part to be shown will be either parallel or at right angle to the film, and the central ray will be directed at right angles to this part. Effects from magnification or distortion of parts when reproduced in the particular arrangement of spot, body and film are considered. The anatomical drawings by Alfred Feinberg are excellent.

Instruction in diagnostic interpretation of films is, properly, not included.

Ethics in radiology, applicable to technicians, are pertinent and sensible. Care of apparatus and equipment, handling of patients, and manners and conduct under different circumstances, as in contagious or isolation wards, operating rooms, and with minor surgical procedures, are clearly set down. The preparations required for special examinations are given.

Photographs of the positions described show only essential objects, tube, table, body part, and supports, with no confusion background. The roentgenogram which should be obtained when the technical performance is perfect is reproduced on the same page with the instructions for each procedure.

These volumes are essential for training and reference in all institutions or laboratories where technical roentgenography is taught or practiced.

J. B. C.

► ROENTGEN DIAGNOSIS OF THE EXTREMITIES AND SPINE - - -

By Albert B. Ferguson, M.D., Associate Professor, Orthopaedic and Fracture Surgery, Boston University. Ed. 2. 519 pages, with 625 roentgen-ray studies and 8 line cuts. 1949, Paul B. Hoeber, Inc., New York. $15.00.

The new edition of this authoritative text and atlas represents a considerable expansion of the old edition in regard particularly to the diagnosis of bone tumors. Further additions have also been made in regard to the spine. The illustrations are numerous and well reproduced. This book represents essentially an atlas since the amount of text devoted to each lesion is relatively small.

L. G. R.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

The 1949 Year Book of Medicine. Edited by Paul B. Beeson, M.D.; J. Burns Amberson, M.D.; George R. Minot, M.D., S.D., F.R.C.P. (Edinburgh and London); William B. Castle, M.D., S.M. (Hon.) Yale M.D. (Hon.) Utrecht; Tinsley R. Harrison, M.D., and George B. Eusterman, M.D. 831 pages, illustrated. 1949, The Year Book Publishers, Chicago. $4.50.

A Synopsis of Medicine. By Sir Henry Letheby Tidy, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.), Extra Physician to H. M. The King; Consulting Physician to St. Thomas' Hospital; Hon. Major-General, lately Consulting Physician to the British Army. Ed. 9, revised and enlarged. 1243 pages. 1949, The Williams and Wilkins Company, Baltimore. $7.00.

1949 Year Book of Radiology. Edited by Fred Jenner Hodges, M.D., Professor and Chairman, Department of Roentgenology; John Floyd Holt, M.D., Associate Professor, Department of Roentgenology; and Isadore Lampe, M.D., Associate Professor, Department of Roentgenology, University of Michigan. 453 pages with 393 figures. 1949, Year Book Publishers, Inc., Chicago. $6.50.

The Development of Gynaecological Surgery and Instruments. By James V. Ricci, M.D., Clinical Professor of Gynaecology and Obstetrics, New York Medical College; Attending Gynaecologist, City Hospital, New York; Consultant in Gynaecology and Obstetrics, Beekman-Downtown Hospital; Director of Gynaecology and Obstetrics, Columbus Hospital. 594 pages, illustrated. 1949, The Blakiston Company, Philadelphia & Toronto. $12.00.

Stedman's Medical Dictionary. Edited by Norman Burke Taylor, M.D., F.R.S.C., F.R.C.S. (Edin.), F.R.C.P. (Can.), M.R.C.S. (Lon.), University of Western Ontario; in collaboration with Allen Ellsworth Taylor, D.S.O., M.A. Ed. 17, revised. 1361 pages, illustrated. 1949, Williams & Wilkins, Baltimore. With thumb index, $8.50; without thumb index, $8.00.

Atomic Medicine. Edited by Charles F. Behrens, M.D., Captain, MC, U.S. Navy; Director, Atomic Defense Division, Bureau of Medicine and Surgery, Navy Department; Medical Officer in Command, Naval Medical Research Institute, National Medical Center, Bethesda, Maryland. 416 pages, illustrated. 1949, Thomas Nelson & Sons, New York, Edinburgh & Toronto. $7.50.

Diseases of the Aorta; Diagnosis and Treatment. By Nathaniel E. Reich, M.D., F.A.C.P., Associate in Medicine, Long Island College of Medicine; Attending Cardiologist, Harbor Hospital, Brooklyn; Associate Attending Physician, Kings County Hospital; Senior Cardiologist, Veterans' Administration, Brooklyn. 288 pages, with 60 figures. 1949, The Macmillan Company, New York. $7.50.

Fractures. By Paul B. Magnuson, M.D., F.A.C.S., Professor of Bone and Joint Surgery and Chairman of the Department, Northwestern University Medical School; and James K. Stack, M.D., F.A.C.S., Assistant Professor of Bone and Joint Surgery, Northwestern University Medical School, Chicago. Ed. 5. 537 pages, with 323 illustrations. 1949, J. B. Lippincott Company, Philadelphia, London & Montreal. $7.00.

Human Pathology. By Howard T. Karsner, M.D., LL.D., Former Professor of Pathology, Western Reserve University; Medical Research Advisor to the Bureau of Medicine and Surgery, United States Navy. Ed. 7. 927 pages with 562 illustrations in black and white and 22 subjects in color on 14 plates. 1949, J. B. Lippincott Company, Philadelphia, London & Montreal. $12.00.

Electrotherapy and Light Therapy; With Essentials of Hydrotherapy and Mechanotherapy. By Richard Kovacs, M.D., Professor of Physical Medicine, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State and Columbus Hospitals; Consultant in Physical Medicine, Surgeon General, U.S. Department of the Army. Ed. 6. 739 pages, with 368 illustrations and 1 plate in color. 1949, Lea & Febiger, Philadelphia. $10.00.

A Manual of Physical Therapy. By Richard Kovacs, M.D., Professor of Physical Medicine, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State and Columbus Hospitals; Consultant in Physical Medicine, Surgeon General, U.S. Department of the Army. Ed. 4. 328 pages, with 124 illustrations. 1949, Lea & Febiger, Philadelphia. $3.75.

Bone and Joint Radiology. By Emerik Markovits, M.D., Formerly Scientific Collaborator of the Central Radiologic Institute of the General Hospital (Holzknecht-Institute), Vienna; Head of the Radiologic Department of Elizabeth Hospital of the City of Budapest; Post-graduate Lecturer at the Central Radiologic Institute of the University of Budapest; Radiologist at the Steiner Cancer Clinic, Atlanta, Ga. 446 pages, with 616 figures. 1949, The Macmillan Company, New York. $20.00.

Malaria; The Biography of a Killer. By Leon J. Warshaw, M.D. 348 pages. 1949, Rinehart & Company, Inc., New York. $3.75.

Atlas of Surgical Operations. By Elliott C. Cutler, Late Mosely Professor of Surgery, Harvard University, and Chief Surgeon of the Peter Bent Brigham Hospital, and Robert M. Zollinger, Professor and Chairman of the Department of Surgery, College of Medicine, Ohio State University, and Chief of the Surgical Service of the University Hospitals, Ohio State University. Illustrated by Mildred B. Codding, A.B., M.A. Ed. 2. 225 pages. 1949, The Macmillan Company, New York. $9.00.

Vision; Its Development in Infant and Child. By Arnold Gesell, M.D., Frances L. Ilg, M.D., and Glenna E. Bullis; Assisted by Vivienne Ilg, O.D., and G. N. Getman, O.D. 329 pages, with 72 figures. 1949, Paul B. Hoeber, Inc., New York. $6.50.

Amputation For Vascular Disease With Refrigeration Anesthesia

GERALD H. PRATT*

ST. VINCENT'S HOSPITAL, NEW YORK

AMPUTATIONS for vascular disease have had high morbidity and mortality rates of 20 to 50 per cent. A technic incorporating certain preoperative, operative, and postoperative principles when combined with refrigeration anesthesia has reduced the mortality to 9.8 per cent in 223 amputations (including 17 amputations for embolism, which had a mortality of 40 per cent).[1]

These technical points are:

1. Careful skin preparation (three separate soap and water cleansings).
2. Antibiotics in massive doses.
3. Adequate diabetic control and chemistry balance.
4. Simplified operative technic with no flaps over the ends of the bone, closure of the skin and superficial fascia *only*, aspiration of the vein for clots.
5. Stockinette extension and no wound dressing for two weeks.
6. Immediate ambulation and rehabilitation.
7. REFRIGERATION ANESTHESIA.

*Chief of Vascular Clinic, St. Vincent's Hospital, New York.

[1]PRATT, GERALD H.: Surgical Management of Vascular Diseases. Lea & Febiger, 1949, Philadelphia.

This feature was adapted from film No. 182 of the Davis & Geck, Inc. Surgical Film Library and the illustrations reproduced with their cooperation and permission.

Refrigeration anesthesia. Thigh amputation. Leg immersed completely in cracked ice for three hours. Elevation eliminates the necessity for a tourniquet. Leg removed from ice in operating room.

Skin incision. This is made at the midpatella level with slightly longer anterior than posterior flap.

Skin and superficial fascia raised for a distance of one and one-half inches.

Muscles divided at the tendinous site one and one-half inches above the skin incision. Major vessels isolated and divided. Femoral vein opened and any thrombus removed and the vein aspirated.

Sciatic nerve injected with novocain to reduce shock accompanying its division. Nerve divided last after ligating it on tension with a fine steel wire (#36). Less phantom pain after this technic than with injection or plastic methods.

Femur divided one inch above site of muscle division. Rough edges rongeured. Hemostasis secured.

Closure of **skin and superficial fascia only,** with three or four interrupted steel wire sutures. This permits drainage, avoids pockets, and produces primary healing in 85 per cent.

Stockinette held to skin by adherent solution protects dressing and permits immediate extension. No dressing for two weeks.

CALF AMPUTATION

Calf amputation may be considered: (1) in younger individuals; (2) where infection is minimal or controlled; (3) if the patient has had an adequate sympathectomy.

Skin incision 8 inches below tibial tuberosity with patient on abdomen.

Skin and superficial fascia similarly raised with posterior flap slightly longer than anterior. Muscles divided in similar fashion. Vessels isolated, veins explored for clots and ligated.

Tibia divided two inches above skin incision and fibula one inch above tibia. Anterior third of each bone beveled.

Closure of skin and superficial fascia *only* with three interrupted steel wires. Stockinette extension and immediate ambulation.

REHABILITATION

Active exercises begin at once. Flexion and extension against counter weights restore muscle tone. Exercises for the three other extremities are included.

"Walker" support permits early and regular ambulation. Artificial limb attached when wound is healed. Patient takes own bath and care of personal requirements.

Crutches are provided at once and precede independent walking. Patients' fear is not the loss of the limb but the loss of their independence. Removal of dependency on others by requiring them to care for all their own needs is a basic and most important factor in the success of the rehabilitation program.

Medicine in Portugal

ANTONIO E. MENDES FERREIRA

SURGEON, CIVIL HOSPITALS AND COLONIAL HOSPITAL, LISBON, PORTUGAL

The evolution of medicine in Portugal closely followed the political, economic, and social life of the country until the foundation of the University of Lisbon in 1288.

Until the middle of the fifteenth century, the Arabian influence, which then dominated the Iberian Peninsula, also made itself felt in medicine. In that period three public assistance institutions were founded which provided great stimulus to the scientific and technical development of medicine in the Peninsula: Todos os Santos (All Saints' Hospital) (1479) (Figure 1), which included nearly all the hospitals of Lisbon, the Hospital das Caldas (1495), and the first "Misericordia" (1498).

The idea of the "Misericordias"—which still persists—was conceived by Friar Miguel de Contreras, and put into effect by Queen Eleanor. The chief aim was to provide assistance to everyone regardless of means.

During the fifteenth and beginning of the sixteenth centuries—the Golden Age of Portugal—Portuguese medicine made rapid strides. Until the eighteenth century the interchange of medical knowledge and foreign influence came primarily from the Latin schools (Italian, French, and Spanish), but in that century the influence of the English school became more important.

In that period university reform was carried out, and at the end of the first quarter of the nineteenth century the Polytechnic School was founded (1824).

The Royal Schools of Medicine and Surgery were created in Lisbon and in Oporto in 1805, followed in 1892 by the Camara Pestana Institute—the center of scientific investigation and of the fight against rabies—which is still the best in the country.

From the end of the last century and during the first quarter of the present, the French and German schools exercised great influence on the study and practice of medicine in Portugal, not only because the great proportion of foreign medical works generally read by us came from those two countries, but because almost all those doctors who had greater aspirations studied there.

During the past twenty years, however, the majority of doctors have taken specialized training in Anglo-Saxon lands, notably in the United States, either through their own initiative or as holders of scholarships or bursaries provided by national organizations (The Institute for Higher Culture) or foreign (Rockefeller Foundation, Mayo Foundation, British Council, etc.).

Medical instruction in Portugal is provided in the three Universities of the country: Lisbon, Oporto, and Coimbra (Group A) and in the School of Medicine and Surgery of Goa (Portuguese India) (Group B).

After they have completed their studies in primary and secondary education and passed an aptitude examination, students are admitted to a university. Only after successful completion of the "Medical Preparatory Course" can the students enter the Faculties of Medicine, the courses of which are six years in length.

Having finished the medical course, students receive a Bachelor Degree, which corresponds to the American "M.D." and entitles the holders to practice. A great number of doctors remain in the hospitals of the University Centers for a period of two years to obtain greater practical experience, and afterwards practice in the Provinces.

Those who intend to have clinical practices in the large cities generally go through a four-year Hospital Course for Interns (similar to residencies).

There are three types of hospitals: (a) Hospital Schools or Universities, belonging to the Faculties of Medicine, with teaching staffs of professors and assistants of the various faculties; (b) The Civil Hospitals of Lisbon, largest hospital organization in the country, incorporating six hospitals, of which the technical staff comprises doctors, surgeons, and specialists who, after having completed their Complementary Hospital Course for Interns, have been accepted in open competitive examinations; (c) The "Misericordias," which constitute the provincial hospitals, whose technical staffs consist of doctors appointed by a competition based on their documentary references.

In all the hospitals there are free consultations for in- and outpatients, general practitioners and specialists working on a part-time basis, generally in the mornings, and looking after their private practices in the afternoons.

In Lisbon, in addition to the Civil Hospitals and the University Hospital, there are the Hospitals of the Army and Navy, a Colonial Hospital for the treatment of colonial diseases which is attached to the Institute of Tropical Medicine, and the Institute of Oncology for the study and treatment of cancer, to which is attached a modern hospital.

The National Institute for the Assistance of the Tuberculous which cares for tuberculous patients through its country-wide system of dispensaries also seeks out cases and where necessary sends them to sanatoria. This body also directs the Maritime Hospitals for the treatment of tuberculosis of the bones.

Problems of hygiene and public health are in charge of the General Administration of Public Health. Ricardo Jorge, distinguished epidemiologist and former President of the Hygiene Department of the League of Nations and of the International Office of Hygiene, was responsible for the extension of hygiene studies in Portugal. It has been in this department of the Health Services that there has been the greatest collaboration with the Rockefeller Foun-

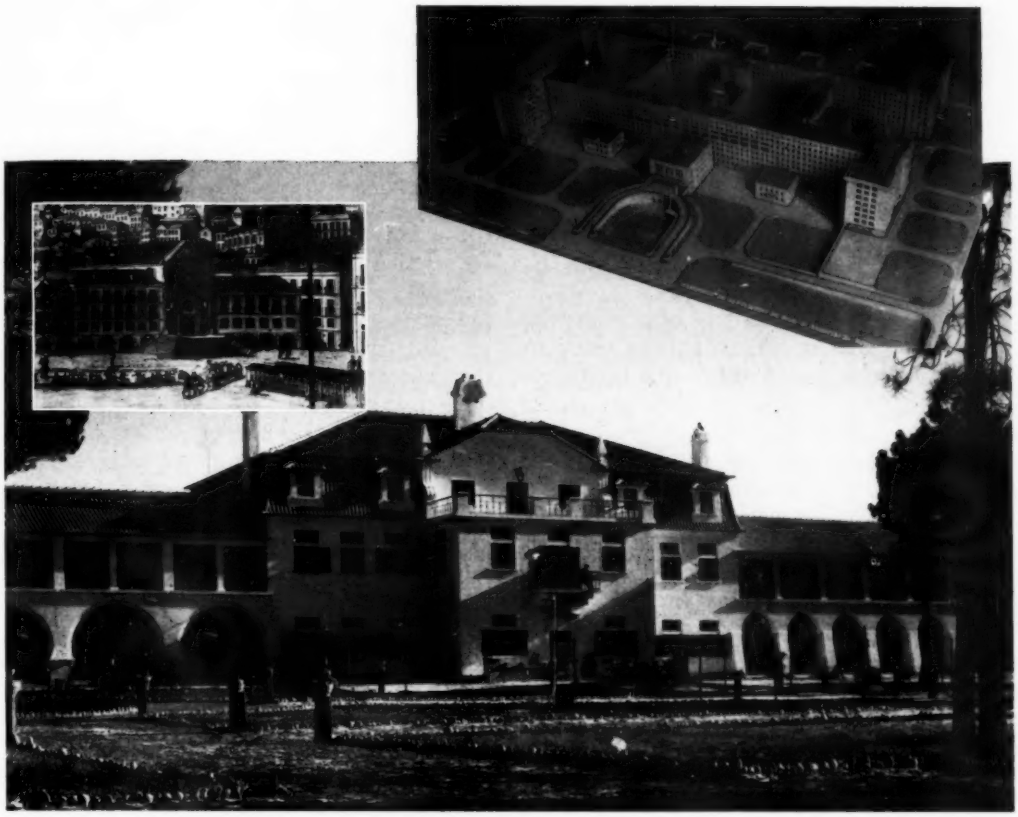

FIGURE 1 *(Insert, left)*. Todos os Santos (All Saints' Hospital) built in 1479. FIGURE 2 *(Insert, right)*. Model of hospital buildings under construction—the University Hospitals of Lisbon and of Oporto. FIGURE 3. Agricultural Hospital Colony of Rovisco Pais for lepers.

dation, especially on problems connected with antimalarial measures and nutrition.

All the general organization of the Medical and Assistance services is under the direct control of the Ministry of the Interior, except the University Hospitals, which are direct dependents of the Ministry of Education, through their coordinating organizations which are: (a) General Administration of Relief, (b) General Administration of Public Health, and (c) General Administration of the Civil Hospitals of Lisbon.

Recently, three important reforms have been carried out: (a) Reform of the Assistance Services of the country, which has conferred a greater measure of administrative autonomy to the "Misericordias" and has given them more extensive possibilities of economic action.

(b) Hospital Reorganization, in which the country is divided into three zones with three types of hospitals: Council Hospitals (General Medical Services), Subregional Hospitals (with some specialized services), and Regional Hospitals (of the kind termed polyclinical), which are generally in the district capitals. At present there are two large hospital blocks in a state of well advanced construction—the University Hospitals of Lisbon and of Oporto (Figure 2).

(c) The Reorganization of the Psychiatric Assistance Services, in which the country is divided into three zones: the North, with the Conde Ferreira Hospital in Oporto; the Center, with the Sena Hospital in Coimbra; the South, with the Julio de Matos Hospital in Lisbon. There have also been founded the Psychiatric Assistance Dispensaries, which classify patients, and when necessary, send them as inpatients to the hospitals named above.

In conclusion, we would say a few words about an institution which, to a noteworthy extent, honors Portugal, and this is the Agricultural Hospital Colony of Rovisco Pais for all lepers in the country. This institution is considered one of the most modern and best equipped in the world (Figure 3).

EDITORIALS

ALLERGY

Even though the percentage of persons who exhibit definite clinical allergic reactions has been estimated to be but a small proportion of the general population, any of the remaining normally nonallergic individuals may at some time manifest sensitivity in some degree. In a recent discussion of allergy,[1] Prickman of the Mayo Clinic stated that "the allergic reaction, if it occurs, is a matter of threshold and other circumstances which vary greatly from one person to the next. The threshold is lowest in allergic patients who are acutely sensitive to such common antigens as pollens, animal danders, feathers, foods, dusts, and drugs, and possibly to certain physical agents such as drafts, cold, and sunlight."

It is now quite generally agreed that the allergic reaction differs only in degree, not in kind, from the normal reaction, the allergic response serving as a warning of a threat to the body's normal processes.

The allergic reaction is described by Swartz[2] as a "protective mechanism gone wrong . . . a heightened physiologic response of the organism to threat. The heightening of this response takes the form of over-dilatation of the small blood vessels with a corresponding increase in their porosity."

Though there may be an inherited predisposition to the allergic response—"atopy"—allergy itself is not an inherited disease. Swartz defines the distinction between atopic and nonatopic persons as "depending on the variation which exists in every single social and biologic characteristic of individuals and prevents the existence of human beings who are identical in any respect. In those individuals in whom cellular reactivity is great, the frank, so-called hereditary allergies appear; in those in whom it is of lowest degree, symptoms of allergy may never appear. Between these two extremes are varying degrees of cellular reactivity and probably of allergic symptoms."

The allergic reaction is most commonly manifested in the skin and mucous membranes, but the symptoms may be referable to any part of the body and quite frequently the reactions may shift from one "shock organ to another" in response to the same or different antigen. As a general rule, too, the allergic reaction involves more than one site in the body.

Although there is as yet no single, universally accepted concept of the cause and treatment of allergy, the physician has a wide choice of more or less effective therapeutic procedures which may be followed to alleviate allergic symptoms and reactions. Most experts agree, however, that the first principle of treatment is the avoidance, as far as possible, of exposure to antigenic agents. It is extremely important that each case be treated individually after careful study of the patient's symptoms and patterns of reaction.

It is becoming increasingly evident, too, that many disease conditions, not previously associated with the concept of allergy, apparently involve a form of allergic response in the body processes. As research progresses in this direction, newer and more effective, as well as more practicable, methods of treating the allergic patient will undoubtedly result.

[1] Prickman, Louis E.: General principles of allergy and hypersensitivity. Proc. Staff Meet., Mayo Clin. 24:431 (August 17) 1949.

[2] Swartz, Harry: Allergy: What It Is and What To Do About It. 1949, Rutgers University Press, New Brunswick, N. J.

POLIOMYELITIS VIRUSES

Investigative studies on poliomyelitis indicate that not one but several strains of viruses, with different immunologic properties, are responsible for the disease. Furthermore, each immunologic type apparently provokes a different pattern of immunity response in the hosts, so that the animal or man infected with one type is not immune to others.

Results of experiments conducted by Bodian, Morgan, and Howe[1-3] at Johns Hopkins University show that infection with one immunologic type of polio virus will not prevent subsequent infection with another unrelated type. Though it has been demonstrated that monkeys can be infected experimentally a second time, the evidence suggests that second infections are possible only when a strain of virus different from the first infecting strain is used. The incidence of such double attacks is, however, relatively small, and the time interval is generally long.

In the experiments, four groups of monkeys were inoculated, each group with a different strain of polio virus. The convalescent animals of each group were divided into four subgroups, and each of these received a reinfecting dose in the brain with one of the four strains originally used.

It was impossible to produce a second attack in monkeys challenged by the same immunologic type of virus as the one used in the initial infection. But when an unrelated type was used, a total of 50 per cent of successful second attacks was recorded.

The initial attack did appear to confer some degree of cross immunity to the monkeys. Moreover, the clinical symptoms were invariably milder in the second attack as compared to the first, and the incubation period was significantly prolonged.

From these findings it can be concluded that in human poliomyelitis a second attack very likely results from contact with an immunologically different type of virus. The studies have also indicated that vaccination with active virus can immunize monkeys against second infection with the same or immunologically related strain of virus.

After a study of 14 strains of polio virus, Bodian, Morgan and Howe were able to group these strains into three basic immunologic types. Similar findings have also been reported by Kessel and Pait[4] of the University of Southern California.

The California researchers have found that the immunity in monkeys obtained by vaccination against homologous virus appeared to be absolute. Not a single monkey succumbed when challenged by the same virus used in vaccination. All monkeys inoculated with the mixture of virus plus specific antiserum were protected, indicating that the vaccinated animals had developed a significant degree of antibodies.

These reports emphasize the fact that a full understanding of the immunologic inter-relationship among various types of viruses is necessary to successful control of the disease and that such vital matters as a simple diagnostic test and a practical vaccine depend upon completion of this work.

1. Bodian, David: Differentiation of types of poliomyelitis viruses. I. Reinfection experiments in monkeys (second attacks). Am. J. Hyg., March, 1949.
2. Morgan, Isabel M.: Differentiation of types of poliomyelitis virus. II. By reciprocal vaccination-immunity experiments. Am. J. Hyg., March, 1949.
3. Bodian, David, Morgan, Isabel, and Howe, Howard: Differentiation of types of poliomyelitis viruses, III. The grouping of 14 strains into 3 basic immunologic types. Am. J. Hyg., March, 1949.
4. Kessel, John, and Pait, Charles F.: Differentiation of three groups of poliomyelitis virus. (Preliminary report.) Proc. Soc. Exper. Biol. & Med. February, 1949.

CARCINOGENIC AGENTS

No one factor is apparently involved in the production of any kind of cancer, according to a report on carcinogenic agents presented by Dr. Harold Rusch.*

Noteworthy among the developments in the study of lung carcinogens has been the discovery that 0.25 ml. of a 10 per cent solution of urethane injected, subcutaneously or peritoneally, into

*University of Wisconsin Symposium on "The Chest," June, 1949.

albino mice, caused an increase in the incidence of tumors from less than 5 per cent in the controls to more than 75 per cent in the treated animals.[1] The tumors were multiple benign adenomas. More recent results have shown that only one injection will produce tumors.

Although the incidence of carcinoma of the lung has been increasing steadily—especially in men—it is difficult to know whether this increase is real or relative, stated Dr. Michael DeBakey in addressing the Wisconsin meeting. That is, there is some doubt as to whether the numerical increase in reported cases of carcinoma of the lung is due to improved methods of diagnosis and record-keeping or whether there has actually been a rise in the incidence of the disease.

In other studies on the carcinogenicity of various agents described by Dr. Rusch, mice were subjected to tobacco smoke, road dust, and tars. Although results are still inconclusive, tobacco smoke blown over the mice seemed to have no carcinogenic effect over varying periods of time. When subjected to road dust, the incidence of lung tumors rose from 7 to 20 per cent for the controls to 47 to 80 per cent when road dust was used.[2]

[1]Nettleship, A., and Henshaw, P. S.: Induction of pulmonary tumors in mice with ethyl carbamate (urethane). J. Nat. Cancer Inst. 4:309-319 (December) 1943.

[2]Campbell, J. A.: Effects of exhaust gases from internal combustion engines and of tobacco smoke upon mice, with special reference to incidence of tumors of the lung. Brit. J. Exper. Path. 17:146-158 (April) 1936.

A. E.

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Consultation Service

This special consultation information service is offered as a regular monthly feature of *Postgraduate Medicine*. Readers are invited to call on this Service for answers to difficult medical problems from members of our Editorial Board and our Editorial Consultants best qualified to help. Each question will be answered by mail and those of general interest will be published each month. Address all communications to Consultation Service, *Postgraduate Medicine*, 516 Essex Building, Minneapolis 3, Minnesota.

PROCAINE REACTION

QUESTION: Does the literature report any case of procaine reaction following the injection of procaine penicillin? Is it possible that such a reaction occurs and what would be its treatment?

M.D.—Connecticut

ANSWER: One must recognize the theoretic possibility that a person may be sensitive to procaine and therefore react to procaine penicillin. On the other hand, in the literature to date there have been no clear-cut examples of sensitivity to procaine after the use of procaine penicillin.

In the event that a reaction attributable to procaine occurred, the treatment would be the same as that which would be used for sensitivity to procaine; namely, the intravenous use of pentothal sodium.

DIFFERENTIAL DIAGNOSIS OF CELIAC DISEASE

QUESTION: What findings are helpful in differential diagnosis of celiac disease from fibrocystic disease of the pancreas and other causes of steatorrhea in children? What is the present view of the cause of celiac disease?

M.D.—Wisconsin

ANSWER: Steatorrhea, or excess fat in the stools, is not an uncommon finding in children. It can be reliably diagnosed only by microscopic examination or quantitative chemical estimation of fecal fat. It can be suspected, however, when the stools are bulky, pale, greasy or frothy, offensive in odor.

Steatorrhea results from any condition which interferes with either the digestion or absorption of fat, such as exclusion of bile from the intestinal tract in any form of obstructive jaundice or exclusion of pancreatic juice from any cause; also when fat is not absorbed due to excess formation of insoluble soaps or long-chain fatty acids, when intestinal motility is excessively increased as in intestinal allergy or disease of the bowel, when there is obstruction to lymphatic drainage by tumors or enlarged lymph nodes; or steatorrhea may be of the idiopathic type which is termed celiac disease.

The two common forms in young children, namely those due to celiac disease and to fibrocystic disease of the pancreas, may easily be confused clinically, but must be differentiated if appropriate treatment is to be administered.

Helpful points are these: pancreatic deficiency manifests itself in the first few weeks or months of life, while celiac disease rarely occurs before 10 months of age. While in celiac disease upper respiratory tract infections are common, we do not see the chronic bronchitis progressing to bronchiectasis which is characteristic of pancreatic disease. Final proof of pancreatic disease must always await demonstration of deficiency of pancreatic enzymes in the duodenal contents obtained by aspiration. Other findings such as low blood cholesterol, low vitamin A absorption curve, clumping of barium in roentgenograms, and flat oral glucose tolerance curve, may be found in either condition.

Celiac disease might better be termed celiac syndrome, since the typical picture may result from a variety of disturbances, such as a primary defect in absorption of carbohydrate and fatty acids, starch intolerance, mechanical obstruction to the pathways of absorption, pancreatic insufficiency, and probably other as yet undetermined causes.

A. WILMOT JACOBSEN

HEMOPHILIA OF THE NEWBORN

QUESTION: Is there any method of diagnosis of hemophilia of the newborn other or better than measuring the coagulation time of the blood?

M.D.—Tennessee

ANSWER: This is an extremely rare disease and when it is present it seldom manifests itself clinically in the newborn period. The coagulation time is prolonged in all cases at the time they are having symptoms, but may be either normal or only slightly prolonged at other times, so a single estimation of coagulation time might not be diagnostic.

Other more common causes of bleeding in the newborn period must first be ruled out before considering hemophilia unless it is a male infant with a family history of a bleeding tendency in other male members of the family, and even then it must be remembered that a baby with a hemophiliac family history is more likely to have manifestations of hemorrhagic disease of the newborn than he is to have bleeding due to hemophilia in the newborn period.

A somewhat prolonged coagulation time is physiologic in the first four days of life with a spontaneous return to normal by the fifth or sixth day. A coagulation time that continues to be substantially prolonged after that time in a male infant might be due to hemophilia. If, in addition, the bleeding time is normal,

the prothrombin time is normal, and the platelet count is within normal limits and clot retraction is good, then a consideration of hemophilia would be in order.

The failure of the blood to clot in the hemophiliac patient is still not clearly understood. Two factors are claimed to be causative: (1) the platelets are resistant to disintegration and therefore qualitatively deficient though quantitatively adequate; (2) the plasma is deficient in a certain necessary globulin fraction.

ARTHUR H. PARMELEE

TREATMENT OF TRICHOMONIASIS

QUESTION: How do trichomonads gain entry into the human body? What is the best method of treatment of trichomoniasis?

M.D.—Missouri

ANSWER: The mode of entry of trichomonads into the human body has not been established. A large proportion of women are obviously carriers of the organisms for years, and have no trouble until some disturbance in vaginal physiology, either primary or secondary, allows them to get a foothold, multiply, and cause general vaginal inflammation. In this respect the infection is much like "trench mouth." It is the impression that most of the carriers may be detected by a consistent spot or small area of vaginitis high in the vaginal vault.

There are many treatments and most of them are successful in most patients. A small residue are resistant to cure by any one method. The program of treatment is more important than the drug used Some such directions as the following for the use of Floraquin (Searle) popularized by Karnaky, should be mimeographed and furnished the patient.

1. Insert the tablet prescribed, one each night at bed time. The tablet must be placed *high* into the vaginal vault behind the cervix. This is usually done best in a standing position with one foot elevated on a footstool or similar object.

2. Use no douches while inserting the tablets. Insert one tablet each night for one week.

3. After one week begin to use vinegar douches, one cup of vinegar to two quarts of water.

4. Repeat course of tablets after one week, if necessary.

5. Whether well or not use the tablets for at least four to five days after each menstrual period for three months.

6. If the above program does not clean up the discharge, the vagina should be scrubbed with tincture of green soap and water before starting course of tablets. This can be done by fastening a gauze square with a rubber band or string to the douche nozzle and scrubbing the vagina thoroughly with the soap.

An alternate program used sometimes in mild cases, or in those who cannot insert the tablets, or in some instances as a trial in cases resistant to Floraquin, consists of a vaginal douche of an 8 per cent zinc chloride solution twice daily for the first week and once daily for the second week. This solution is made by mixing 50 gm. in 150 cc. of distilled water and using one tablespoon of this to a quart of warm water as the douche. This latter treatment was reported by J. Novak *(Urol. & Cutan. Rev.* 50:80, 1946).

ROBERT L. FAULKNER

ENURESIS IN CHILDREN

QUESTION: In the treatment of enuresis in children, have any drugs proved helpful?

M.D.—Indiana

ANSWER: Drug therapy is of little value in the treatment of enuresis. Some years ago atropine or belladonna was a favorite form of therapy, but more recently it has been largely abandoned as the psychiatric implications of the problem have been better understood.

In approaching the problem of enuresis in a child, one should first determine whether or not there is an organic basis for the condition. If this can be excluded, psychiatric investigation should be instituted. Sibling jealousy, emotional maladjustment, environmental tensions, etc. may be causes of the disorder. Familial inheritance must also be considered. The psychiatric approach probably gives the best results.

LEE FORREST HILL

PROPYL THIOURACIL IN HYPERTHYROIDISM OF PREGNANCY

QUESTION: Could you please send me some data on the use of propyl thiouracil in the treatment of hyperthyroidism of pregnancy? I have seen what I believe to be a cretin as a result of the use of the drug in hyperthyroidism. I have a patient now with hyperthyroidism, in her third month of pregnancy, and I hesitate to use propyl thiouracil in view of what I have seen.

M.D.—New York

ANSWER: There has still been inadequate experience with the use of goitrogens, such as propyl thiouracil, in the treatment of hyperthyroidism during pregnancy to warrant any final opinion concerning the question of possible hazard to the fetus.

It cannot be stated with certainty that serious depression of fetal thyroid function cannot occur when the mother receives a goitrogenic drug. Until this has been clearly demonstrated, the use of goitrogens during pregnancy should either be avoided or should be undertaken with the realization that danger to the fetus is involved. The danger can probably be lessened by the use of the smallest effective dose of the goitrogen.

Thyroidectomy after careful preparation with iodine is a relatively safe procedure during pregnancy in the hands of experienced surgeons and the possibility of inducing abortion is minimal.

The Doctor As Novelist

EDWARD PODOLSKY

BROOKLYN, NEW YORK

THE profession of medicine peculiarly fits the physician for the profession of letters. His practice constantly affords him the opportunity to study and observe a miscellany of human characters and the conditions which formed and sustained each individual type. It was Collins who said: "The novelist is concerned with the psychological details of personality, emotional states, and behavior; the springs of human action must be his incessant study, for his business is to explore human nature and to chart his discoveries, a large part of the physician's life also."

RABELAIS

Among the earliest of the notable medical men who have made names for themselves in the field of letters was Francois Rabelais. Born in 1490 on a farm near Chinon, he was baptized at the neighboring village of Senilly, and received his elementary education there at the Benedectine monastery of St. Peter. At an early age Rabelais was removed from this school and sent as a novice to the Franciscan monastery of La Baumette.

Some time about 1510 Rabelais entered the Franciscan order and while studying for the priesthood acquired a vast fund of classical knowledge which is reflected in his works. After his ordainment, Rabelais traveled a great deal and studied law during a stay in Bourges. He later came to Orleans where he spent much time in the company of a group of roistering students.

Seized by wanderlust again, Rabelais reached Montpellier where he matriculated as a medical student on the 17th of September, 1530. Rabelais proved a brilliant student, received his M.D. and was off on his wanderings once more. He arrived at Lyons and in 1532 was appointed as physician to the hospital of the Hotel Dieu. He was a very competent physician and is said to have reduced the death rate by nearly 3 per cent during his stay in Lyons.

During these years Rabelais was busy both as a doctor and as a writer. In 1532 he published his *Pantagruel,* giving an account of the birth and childhood, life in Paris, and of the subsequent heroic deeds of the prince Pantagruel, son of Gargantua. This novel was a great success, and ran through nineteen editions in Rabelais' time.

Throughout his life Francois Rabelais practiced his three professions: religion, medicine, and letters, serving all three well. He traveled widely, practicing medicine with great distinction and writing prodigiously. Of the last two years of his life very little is known. Not long after resigning the curacies of Meudon and of Jambet in January, 1553, he died. Rabelais' stories are notable because they are a mixture of insane laughter and mock gravity, because they point out the childishness and grandeur of the commonplace. Rabelais was the first great laugher in literature. He saw life in all its sordid details, and yet could not be serious about it.

VON SCHILLER

Pre-eminent among medical literateurs was Friedrich von Schiller, who was born in 1759, and whose plays *The Robbers, William Tell, Marie Stewart, Maid of Athens* are among the greatest in German literature. He was graduated in medicine, and for several years was a military surgeon. However, his success in literature caused him to abandon his medical practice in order to devote more time to his novels and dramas. Carlyle considered him the finest writer of the 18th century. His comedy, *Faust,* is one of the greatest in all literature.

SMOLLETT

One of the early great English novelists was Tobias Smollett. Smollett was not only a gifted novelist, with a sharp eye for detail, but a physician and surgeon who possessed an extensive knowledge of the medical practice of his time.

Tobias George Smollett was born in Dalquhurn, Dumbartonshire, Scotland. The exact date of his birth is not known, but he was baptized March 19, 1721. He came of a well-known and rather wealthy family. When Tobias was a small child his father, who had failed to inherit any of the family fortune, died, leaving no provision for his young widow and three children. Relatives provided them with a modest income, and Tobias was sent to a good school and later to the University of Glasgow, where he began the study of medicine.

While still at the University, Smollett was apprenticed to John Gordon, a surgeon. The young student obtained a good grounding in medicine and surgery, but before he took his degree the relative who had been supplying funds for his studies died and it became plain that Tobias would have to depend on his own resources from that time on. He was then only 18 years old, but he was a youngster of great determination, and he decided to seek his fortune in London.

Tobias had two methods by which he hoped to earn some money. The one on which he founded his greatest expectations was a tragedy in blank verse called *The Regicide.* If this failed he meant to fall back on his knowledge of surgery. He showed his play to all the leading actors and producers, but they were not in the least impressed, as it was amateurish and far from being a good play.

In 1739, the year of Smollett's arrival in London, war broke out between England and Spain. Preparations were started to dispatch a naval expedition to the West Indies and Smollett decided to seek a commission as surgeon's mate in the navy. For this it was necessary to pass an oral examination at Surgeon's Hall and in his partially autobiographical novel *Roderick Ransom,* published some years later, Smollett gave a caustic picture of that examination. The members of the board began to argue among themselves and the controversy became so heated that the young applicant was almost forgotten. In the end he was hastily passed, having had little opportunity to demonstrate either knowledge or ignorance of medicine.

On March 10, 1740, Smollett was granted a warrant to serve as a surgeon's second mate, and he succeeded promptly in obtaining an appointment on H.M.S. Chichester, one of the largest vessels in the fleet which was being outfitted. On October 26, the fleet sailed for Jamaica where it joined another squadron; and the combined forces set out to attack Cartagena, on the Caribbean coast, in what was then known as New Spain. This attempt proved unsuccessful and the fleet returned to Jamaica, where Smollett was landed with other surgeons to aid in looking after the troops ashore.

Although Smollett lived for several years by his medical practice, this was never large. His failure to build up a successful practice evidently resulted not from lack of ability or knowledge, but because he did not know how to handle patients with kindness and consideration. He had a violent temper; he was extremely blunt in expressing his opinions, and this did not make him very popular with his patients.

In 1747 he was married. His wife, who had inherited a small fortune, rented a large house and the young couple began to entertain a great deal. It was decided that Smollett should complete his medical education and he took his M.D. in 1750 at Marischal College, Aberdeen.

His first novel, *Roderick Ransom,* had already appeared and had attracted favorable attention. It was followed in 1751 by *The Adventures of Peregine Pickle,* which though inferior to *Roderick*

Ransom, was a greater financial success and established Smollett's reputation as a novelist. In the years that followed he not only continued to publish novels but was active in the editing of several magazines, particularly the *Critical Review,* which was long popular, as well as other literary works. His most profitable venture was a *History of England,* which, though it did not win Smollett a lasting reputation as a scholarly historian, appealed to the public taste and had a large sale.

Smollett continued to practice both his professions, writing both fiction and nonfiction. His last and best novel, *The Expedition of Humphry Clinker,* published in 1769, received much favorable notice, and sold well. On September 17, 1771, Smollett died, at the early age of 50.

In his day Smollett was ranked with his contemporary novelists Samuel Richardson and Henry Fielding. His novels have exerted a wide influence and have earned him the right to be regarded as one of the chief forerunners of the modern realistic school of fiction.

BROWN

One of the most popular novels ever written was *Rab and His Friends,* authored by Dr. John Brown, for many years a practicing physician in Edinburgh. John Brown was born September 22, 1810, in the village of Biggar, Lanarkshire, Scotland. When he was 6 years old he lost his mother. His father, though kindly and affectionate but by nature silent, reserved, and wholly absorbed in his work, was much depressed by the loss of his wife. A distant cousin and lifelong friend thought the atmosphere in which the boy and his brother and two sisters spent their childhood was altogether too solemn and joyless. When John was 12 years old, however, his father was called to a church in Edinburgh and there the boy made many friends in school and had a happy and normal youth. He impressed his friends in Edinburgh High School as "frank, good-humored, a little odd, a curious mixture of simplicity and sense, companionable," but "giving little indication of what he afterwards became."

On graduating from high school he entered Edinburgh University and after only a few months of the arts course enrolled as a medical student. The apprenticeship system of medical instruction still prevailed in Scotland; concurrently with his medical course at the university, Brown was apprenticed to James Syme, later to become one of the leading surgeons of his time.

Before taking his degree, John, on the recommendation of Syme, accepted a temporary post as a physician in Chatham, on the southeast coast of England, where he spent a busy but pleasant year. Before returning home he was subjected to a trying ordeal by a cholera epidemic which taxed the physicians of the town to the utmost. The young assistant distinguished himself by his devoted care of his cholera patients.

In 1833 John Brown obtained his doctor's degree and at once began to practice in Edinburgh, a city which he had loved from his first acquaintance with it and which he never afterwards left except for brief periods of travel. In his medical practice he acquired a reputation for close and accurate observation of symptoms, conscientious attention to his patients, and skill and good judgment in their treatment.

In 1840, at the age of 29, he married Catherine McKay. Unlike her husband she was not a universal favorite in society, for she was one of those extremely honest and candid people who do not hesitate to show their own dislikes. But it is worth noting that her husband's most interesting and intellectual friends usually liked and admired her. Her husband's devotion to her never wavered during the twenty-four years of their married life.

Dr. Brown's literary career began almost by chance a few years after his marriage. Occasional letters and paragraphs from his pen had appeared in a popular Edinburgh newspaper, the *Scotsman,* and like everything he wrote they bore the impress of his personality. One morning to his great surprise he received a letter from the editor of a rival paper, the *Witness,* asking him to write some articles on a current art exhibition and enclosing one hundred dollars in payment.

Dr. Brown had always had a keen interest in art and the quick, careless sketches with which he often adorned his letters show that he possessed a certain artistic gift himself; but he felt a great deal of hesitation at undertaking professional art criticism. His wife, however, succeeded in convincing him that he was thoroughly capable of writing the articles. They proved to be the first of a long series of papers on a variety of subjects which appeared in various periodicals and which were reissued in book form under the title of *Spare Hours.*

Dr. Brown's most popular story, *Rab and His Friends,* made its initial appearance in print in the first volume of *Horae Subsecivae,* published separately in 1858. It was reprinted by itself many times. In a preface to the first separate edition, Dr. Brown tells how he came to write it. An uncle, the Rev. Dr. Smith of Biggar, asked him to give a lecture before the Biggar Athenaeum. Dr. Brown had never lectured before and knew that he had no gift for public speaking. However, his uncle insisted and, besides he himself had a strong desire to say something to these people among whom he had spent his childhood, if only he could think of the

right thing to give them. Searching his mind for a suitable topic, he remembered an incident which occurred when he was a medical student and clerk at the small surgical hospital which Syme, his instructor, had founded. He had often thought of it since; "indeed, it came on me at intervals almost painfully," he says, "as if demanding to be told"; yet when he at last tried to write it the words would not come. Then one night after a happy evening with congenial friends, he sat down in his study about midnight and when he rose from his chair at four o'clock in the morning the story was written.

The central incident is a vivid but restrained account of a major surgical operation performed before the advent of either anesthesia or asepsis. The audience which first heard the story did not respond well, owing to the poor style of Dr. Brown's delivery, and it was not until *Rab and His Friends* appeared in book form that he himself had any idea of its wide potential appeal.

Perhaps the most popular of Dr. Brown's writings next to *Rab* was *Marjorie Fleming,* a tender and amusing biographic sketch of a gifted child. Another favorite was the essay entitled *Letter to John Cairns, D.D.* which was really a memoir of Dr. Brown's dead father. The appeal of Dr. Brown's writings lies largely in their revelation of his own personality and in a characteristic blending of gentle humor with the serious or the pathetic.

Dr. Brown continued his medical work and writing almost to the end. The end came rather suddenly in his 71st year and he died May 11, 1882.

LEVER

Another doctor-novelist of that time was Charles Lever, whose novels were as popular in their days as those of Dickens and Thackeray. Lever was born in Dublin in 1806, the son of James Lever, a successful building contractor. As a school boy, Charles was noted for his popularity and his leadership in sports and pranks. He was also quite adept at fencing and dancing. He was never very studious and even when he entered Trinity College, Dublin University he was neglectful in his work, and it took him five years instead of four to get his B A.

Though he planned to study medicine, Charles felt that at 21, he was not yet ready to settle down to serious study. He wanted to see something of the world first and sailed for Canada aboard a ship owned by the father of two of his friends. He traveled widely throughout the unsettled parts of Canada, had many adventures among the Indians, and was adopted into a tribe of Indians whose primitive existence he shared for some time.

After his return to Europe he studied medicine at the universities of Heidelberg and Vienna and completed his medical studies at Trinity College from which he received his medical degree in 1831.

Not long afterward, there was a devastating epidemic of cholera in Ireland and physicians were urgently needed for the remote country districts. Lever offered his services and was sent to County Clare in the west of Ireland. The totally inexperienced doctor made a good record and on his return to Dublin four months later he was offered a permanent post as dispensary doctor at Port Stewart, a small but pleasant watering place. The salary was rather small but he received an additional appointment in a neighboring town. He built up a private practice and in this way he felt that he could support a wife. He married Kate Baker, a petite, pretty girl who shared his taste for a lively social life. Though she made no pretentions to special intellectual accomplishments, she proved herself an excellent critic of his work when he began to write for publication. Throughout his life, he read to her everything he wrote and usually followed her suggestions in making revisions.

Lever had always been a gifted raconteur and while still in college had tried writing stories. Before leaving Ireland, he had contributed articles to the leading Irish literary periodical, the Dublin University Magazine, and had begun writing for it a serial called *The Confessions of Harry Lorrequer.*

As soon as *Harry Lorrequer* was finished, Lever began work on another novel of the same type, *Charles O'Malley.* When his second novel proved a great success, even surpassing in popular demand the current works of Dickens, he felt that he was now a real novelist and gave up his medical practice to devote all his time to writing. He also received an offer to assume the editorship of the Dublin University Magazine at a good salary.

Thereafter Lever wrote daily, producing a series of novels which attained great popularity. Some of his novels dealt with social problems. *The Knight of Gwynne* and *The Martins of Cro' Martin* dealt with the social and political problems of his native land. Charles Lever died June 1, 1872.

New Drugs *and* Instruments

Information published in this department has been supplied by the manufacturers of the products described.

PARADIONE

PURPOSE: Control of the petit mal triad.

DESCRIPTION: Paradione (Paramethadione, Abbott) is a homolog of Tridione, differing only in the substitution of an ethyl for a methyl group on carbon 5.

INDICATIONS FOR USE: Petit mal, myoclonic and akinetic epilepsy. Some patients whose seizures were not controlled by Tridione were afforded control by Paradione, and vice versa.

CAUTION: Paradione is contraindicated in patients with severe renal or hepatic disorders.

DOSAGE AND ADMINISTRATION: Dose must be based on each patient's response. For older children and adults, initial dose is 0.9 gm. daily in divided doses. Patients should be carefully observed and complete blood and differential counts made at intervals of not less than four weeks.

HOW SUPPLIED: Capsules, 0.3 gm., bottles of 100 and 1,000. Solution, 0.3 gm. per cc., 50-cc. bottles with graduated dropper.

PRODUCER: Abbott Laboratories, North Chicago, Ill.

BENADRYL EMPLETS

PURPOSE: Relief of hay fever, asthma, urticaria, and other allergic conditions.

COMPOSITION: Benadryl hydrochloride (diphenhydramine hydrochloride, P. D. & Co.) 50 mg. in an enteric-coated, flame-colored tablet.

DESCRIPTION: The action of the benadryl in the Emplet is delayed, so as to begin action when the effect of the Kapseal dosage is wearing off.

INDICATIONS FOR USE: Concurrent administration with a 50 mg. Benadryl Kapseal on retiring.

HOW SUPPLIED: Bottles of 100 and 1,000.

PRODUCER: Parke, Davis & Company, Detroit 32, Mich.

EURAX CREAM

PURPOSE: Scabicide.

COMPOSITION: Active constituent is N-ethyl-o-crotonotoluide.

DOSAGE AND ADMINISTRATION: The cream is thoroughly rubbed into the skin of the entire body except the face and scalp.

HOW SUPPLIED: 60 gm. tubes and 1-lb. jars.

PRODUCER: Geigy Company, Inc., New York, N.Y.

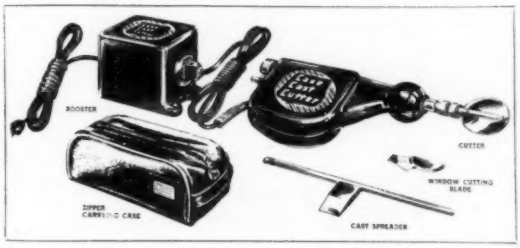
CAUBREN COMPOUND

PURPOSE: Cold combatant.

COMPOSITION: Combination of three drugs—Chlorothen Citrate (25 mg.), acetophenetidin (320 mg.), and caffeine (32 mg.).

DOSAGE AND ADMINISTRATION: Treatment should begin as soon as possible after onset of symptoms—preferably within the first twelve hours.

PRODUCER: Whittier Laboratories, Chicago, Ill.



CASE CAST CUTTER

DESCRIPTION: Electric vibrating tool, weighing one pound, for removal of casts. Pistol grip and counter-balanced weight facilitate one-hand operation. It will not burn or injure underlying skin.

Operating on the principle of cutting by vibration at a speed of 7,200 strokes per minute, the power is increased by means of the booster attachment into which the tool is plugged and which in turn is plugged into the A.C. power supply.

Comes complete with a plastic zipper carrying case, a stainless steel cast spreader (to facilitate cutting stockinette), and an extra blade for cutting windows in casts.

PRODUCER: Produced by the Burgess Battery Company, the Case Cast Cutter is available through the Triple C Products, Inc., 108 S. Genesee Street, Waukegan, Ill.

AUREOMYCIN HYDROCHLORIDE INTRAVENOUS

PURPOSE: To achieve a high therapeutic blood level of aureomycin quickly in cases of emergency or where patients are unable to take oral medication.

COMPOSITION: The package contains one vial of 100 mg. of aureomycin hydrochloride powder and one 10 cc. vial of leucine diluent to make a solution containing 10 mg. of aureomycin hydrochloride per cubic centimeter.

PRODUCER: Lederle Laboratories Division, American Cyanamid Company, Pearl River, N.Y.

THEPHORIN-AC

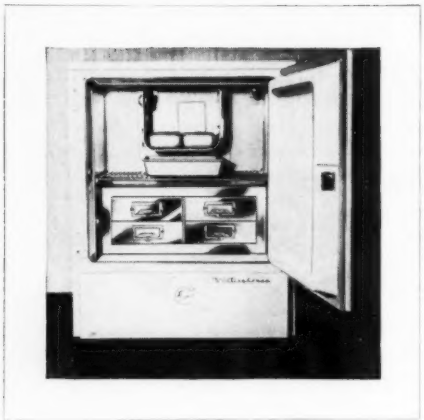
PURPOSE: Symptomatic treatment of the common cold.

COMPOSITION: Contains 10 mg. of Thephorin, 160 mg. of aspirin, 160 mg. of acetophenetidin, and 15 mg. of caffeine.

DOSAGE AND ADMINISTRATION: From 1 to 2 tablets should be taken one to three times daily, depending on the response. Treatment should be started as early as possible after onset of symptoms.

HOW SUPPLIED: In vials of 25 and 100 and bottles of 1,000.

PRODUCER: Hoffmann-La Roche, Inc., Nutley, N.J.



BIOLOGICAL INSERTS

DESCRIPTION: Biological inserts for storage of sera, blood, blood plasma, blood substitutes, toxins, antitoxins, and other medical and pharmaceutical supplies needing refrigeration. The inserts are available for every Westinghouse model refrigerator.

Constructed of chrome steel with chrome steel door. The drawers have perforated cane sides and bottom with solid backs and stop catches to prevent their pulling out. Further information can be obtained from:

PRODUCER: Westinghouse Electric Appliance Division, Mansfield, Ohio.

ALZINOX MAGMAS

PURPOSE: Treatment of hyperacidity and peptic ulcer.

COMPOSITION: Each teaspoonful (5 cc.) of Magma ALZINOX (White) contains:

Dihydroxy aluminum aminoacetate 0.5 gm. (7.7 gr.)

Each teaspoonful (5 cc.) of Magma ALZINOX (Pink) contains:

Dihydroxy aluminum aminoacetate 0.5 gm. (7.7 gr.)
Phenobarbital ..... 8.1 mg. (1/8 gr.)
Homatropine methyl bromide ..... 0.65 mg. (1/100 gr.)

DOSAGE AND ADMINISTRATION: One or two teaspoonfuls one to two hours after meals and upon retiring, or as directed by the physician.

HOW SUPPLIED: 8-ounce bottles.

PRODUCER: The E. L. Patch Company, Boston, Mass.

DIAPARENE*

PURPOSE: Control of ammonia dermatitis in infants and incontinent patients.

DESCRIPTION: A nonvolatile, nonmercurial antiseptic rinse.

DOSAGE AND ADMINISTRATION: For diaper rash prevention, dissolve one tablet in two quarts of water as final rinse, pouring evenly over not more than 6 night diapers at a time. For diaper rash treatment, rinse all diapers. For resistant diaper rash, concentration may be increased as much as five times. Apply DIAPARENE ointment, as a bactericidal, water-miscible adjuvant during the day, between diaper changes. For the incontinent adult, perineal coverings may be soaked in a solution of one DIAPARENE tablet to each pint of water.

HOW SUPPLIED: Packages of 20 and 40 tablets; ointment in 1- and 2-ounce tubes. Clinical dispensing packages are available in 500 and 1,000 tablets; also 1-pound jars of ointment.

PRODUCER: Pharmaceutical Division, Homemakers' Products Corporation, New York, N.Y.

*Trade mark.

FEOSOL *PLUS*

PURPOSE: Treatment of secondary anemias which are ill-defined and resistant to iron alone.

COMPOSITION: Each capsule of Feosol *Plus* contains:

Ferrous sulfate, exsiccated, U.S.P.	200 mg.
Liver concentrate powder (35:1)	325 mg.
Folic acid	0.4 mg.
Thiamine hydrochloride, U.S.P. (B_1)	2.0 mg.
Riboflavin, U.S.P. (B_2)	2.0 mg.
Nicotinic acid (Niacin), U.S.P.	10 mg.
Pyridoxine hydrochloride (B_6)	1 mg.
Ascorbic acid, U.S.P. (C)	50 mg.
Pantothenic acid	2 mg.

DOSAGE AND ADMINISTRATION: One capsule, 3 times daily after meals.

HOW SUPPLIED: Bottles of 100 capsules.

PRODUCER: Smith, Kline & French Laboratories, Philadelphia, Pa.

ANESTHETIC LUBRICATING JELLY

PURPOSE: Intended principally for use as a lubricating agent to facilitate passage of instruments into body cavities, as in cystoscopy and proctoscopy.

COMPOSITION: The jelly represents a specially prepared formulation of chondrus, tragacanth, glycerin, boric acid and water, containing METYCAINE—gama (12-methyl-piperidino) propyl benzoate hydrochloride, Lilly, in a concentration of 1 per cent.

HOW SUPPLIED: Fully sterilized, in 2-ounce tubes with anal applicator.

PRODUCER: Johnson & Johnson, New Brunswick, N.J.

TROCHONS

PURPOSE: Prophylaxis and treatment of minor infections and irritations of the throat and oral cavity.

COMPOSITION: Each Trochon contains 2 mg. of tyrothricin (equivalent to 0.4 mg. of gramicidin), 5 mg. of benzocaine, sweetening and flavoring, q.s.

INDICATIONS FOR USE: Prior to and following tonsillectomy and other operations performed in the throat and oral cavity.

DOSAGE AND ADMINISTRATION: Average dosage is one troche dissolved slowly in the mouth every two to three hours. No more than 8 Trochons should be taken in a day.

HOW SUPPLIED: In vials of 12.

PRODUCER: Ives-Cameron Company, Inc., New York, N.Y.

Leaves from a Doctor's Diary

By Maurice Chideckel

November 1 . . . They were no triad of virtues, the two cousins and the lady, especially the lady, a ravishing brunette named Gwendylin. No. This story is not one of picturesque and apocryphal detail; nor are there morals to celebrate.

The recent operation for a perforated gastric ulcer did not prevent Robert Carver from falling in love with that devastating beauty. He fell and fell hard. It was infatuation at first inspection. He proposed and was accepted. She had never before met a charming man like Robert. Marriage in a week. The night before the wedding he attended a stag in his honor and left his bride-to-be in the custody of his cousin, Morgan Carver. Morgan, too, became hopelessly intoxicated. For her appeal was irresistible. When Robert called for his beloved, he found a note: "Morgan and I went off to be married. Good luck."

Two months ago, Gwendylin was delivered of a "premature" boy, weighing nine pounds, seven months after marriage. Robert swore that he was the father of the child. Morgan countered with the assertion that Gwendylin was innocent and he was the father.

To prove to the world Gwendylin's innocence, a blood examination was made. Blood of Robert, Morgan, Gwendylin and the baby proved one thing conclusively: Neither of the men was responsible for the birth of the boy. "Who is the baby's dad?" I whispered in the lady's ear. She laughed. "Wouldn't you like to know?" A heavy sigh, then: "So would I."

In rushed husband Morgan. "Well, well, yes, yes, what? Tell me." I spoke seriously: "I can assure you now that your cousin Robert is absolutely not the father of the boy." He danced boisterously, "I knew it, oh, how well I knew it."

Well, the inarticulate, the sweet, and the apparent innocent are no better, at times, and can be no more interpreted than a dream. The dream of soft-spoken Evelyn Gould was to be a mother. But the husband! Once a bilateral epididymitis following gonorrhea destroyed the life of the sperm, and fatherhood was banned forever. He is not aware of his deficiency.

Piously and slowly and also sweetly she spoke, without a muscle twitching in her fine face: "My dream of motherhood. Has that dream fled? Decidedly no. I shall have a baby. No, no, no. No artificial insemination. Shocking." She added lipstick to her lips and continued: "Not all men's seeds are lifeless. What? Divorce my husband? Preposterous. I love him and we are happy. And I shall make his happiness supreme by bringing him a child. You'll deliver me, won't you? Good day, doctor."

Once, while visiting a mental hospital, a woman from outside mistook me for an inmate and asked how long I was confined to the asylum, and whether I liked it there. Told that I was a visiting physician, she apologized and assured me that from this day on she'll never judge one by appearance. Neither will I.

* * *

November 5 . . . The uterine fibroma from the country woman, sent in for immediate operation because of the dyspnea and edema of extremities, came out shrieking loud. The placenta followed soon after. Don't ridicule that country doctor. The excess of liquor amnii, exceeding 6 pints, made it impossible to detect the fetal heart. The young mother too denied the possibility of being "that way." More experienced men than the young medico from the backwoods mistook fibroma for pregnancy when there was excessive hydramnios.

The young mother's malapropism kept the interns and nurses roaring. Was she hungry? "No. I am not at all inquisitive. The doctor who diagnosed a tumor in my vitality misconcerned me." How does she feel? "Some displeasure in the belly, but it is flexible," meaning intermittent. "I am obliged to my husband," she told me, "for his exaltation," meaning achievement. I told her that this was not an original idea, and one need not be a genius to become a father. She smiled and thanked me for my "sobriety."

But the conviviality of the young farmer was contagious and even enchanting. A name for his daughter? "Helen? No. Suppose some day she marries a man who stammers? What was the name of that tumor my wife was supposed to have? 'Fibroma.' Great. A beautiful name, Fibroma Richardson. The only name in both the Carolinas." And in the universe.

* * *

November 7 . . . The forces of

change, so it was said, are more powerful than those of permanence. But some things are eternal, and never do change, prejudice, for example. The hope that the human race, a heterogenous mixture, will one day become a social and racial homogeneity, will, it seems, never come to realization.

Apropos of Milton Drake, a refined and cultured man admitted to the ward for a virus infection. He was allergic to every antibiotic and Dr. Green decided on bacitracin. The allergic manifestations were severe. It was ward round time and as nurses and interns crowded around him, Green remarked that this was the first time he saw allergic reaction in a white man. All the unpleasantness following the administration of bacitracin was in Negroes.

He turned to the patient: "One would suspect you have Negro blood in you." The sick man nodded assent. His father, a white man, married a mulatto girl. His mother is almost white. It's hard to depict the commotion that followed. All heads were turned away. As that particular hospital has no ward for colored patients he was immediately transferred to a hospital that has one. Of all the men in the ward from which he was expelled Drake was the most refined and the most cultured, a Ph.D. from a great university and author of many scientific contributions.

I walked and thought: Hatred because of race and color is no virgin soil for study. Man loves to hate. Man craves to attack and destroy the point of least resistance. The subject of antagonism between races for no cause at all has always been with me an undulled stimulus for study. Little men of no consequence raise their heads in a superior attitude towards those in the minority. Why should one be despised because, by accident of birth, he is what he is? Why should unreasonable people be allowed and encouraged to draw accusation against a whole race or against people of different faith because of one, or of a small group?

I was crossing a very busy intersection with my head up, looking heavenward—an old, bad habit of mine. Brakes screeched and the voice of an angry taxidriver made many turn around: "Hey, mister, if you don't look where you're going you'll go where you are looking."

* * *

November 10 . . . The otosclerosis of Sam Landy, a salesman in a department store, led eventually to complete and hopeless deafness. The boss did not discharge him. He just transferred him to the complaint department.

Dr. James Alger promised complete recovery of the 10-year-old boy with myelogenous leukemia by urethane and nitrogen mustards. When I criticized his assurance in such a fatal disease, he became infuriated. He screamed:

"We are two in this room. One of us is insane. I'll wager one hundred dollars that I am not the one." Now draw your own conclusions as to who is crazy.

* * *

November 16 . . . It was once stated that no writer could equal eccentric Thomas Carlyle in bringing through the medium of words the physical presence of the people he described, for his description penetrated deep beneath the surface appearance.

The one who made the statement did not hear elderly Beatrice Graham depict her son-in-law, his virtues, his devotion to her, and the nobleness of his character. She was assured by said son-in-law, a high school teacher, that she has heart disease. She was at once seized with cardiac pain over the apex, the pain commonly associated with anxiety, and there was dyspnea because of this anxiety.

Mother-in-law Beatrice did not have heart disease, and I assured her that her heart returned to normal. "My son-in-law, God bless him. In two weeks is my birthday. I shall be 52. He already wished me I should live as long as Shakespeare." I did not tell her that that immortal died at the age of 52. So he only wished her two more weeks of life. He thought that was enough.

Time has not changed human gross anatomy, nor human histology, but it did modify man himself. Shakespeare when he left this life at 52 was viewed as an old man. The venerable old man of his century was Lancaster who passed away at the age of 59.

And now. A man of 73 was a prime favorite with many women and was jailed for loving too many at one time and receiving payment for his affection. A patient of 84 has just become the father of a baby. Another one of 88 is building an apartment house to have an income for the future. Today physiologic age and psychologic age are two different entities. Have the cerebral areas really undergone modifications in structure and function?

* * *

The richest and most beautiful experiences in life come through gratitude—so, truly, for the priceless gift of friendship and for consideration shown—*Merry Christmas and a Happy and Prosperous New Year To Everyone.*

SUBJECT INDEX—VOLUME VI

ABDOMEN, acute diseases, 311
Abortion, habitual, stilbestrol in prevention, 82
Acidosis, diabetic: treatment, 83
Acne, rosacea, treatment, 480; vulgaris, stilbestrol treatment inadvisable, 256
Actinomycosis of lungs, 445
Addison's disease, desoxycorticosterone treatment, 329
Adrenals, tumor, pheochromocytoma, 408
Alcoholism, treatment, 320
Allergy, as cause of diarrhea, 4
Amebiasis, as cause of diarrhea, 3; rectal diagnosis, 388; treatment, 255; treatment of amebic dysentery, 180
Aminophyllin, suppositories in treatment of spasmodic croup, 180
Amputation for vascular disease with refrigeration anesthesia, 492
Androgens in treatment of breast cancer, 431
Anemia, megaloblastic, treated wtih vitamin B_{12}, 303; pernicious, *see* Pernicious anemia: secondary to nutritional failure, 97; treatment with intravenous iron, 330
Anesthesia, refrigeration, in amputation for vascular disease, 492
Ankle, painful conditions of foot and ankle, 292
Antibiotics, *see also* Bacitracin, Penicillin, Streptomycin; value questionable in rheumatoid arthritis, 422
Anticoagulants, heparin and dicumarol for cardiac infarction, 330
Apoplexy, in essential hypertension, (facing pages) 48, 136
Apparatus, ileostomy bags, 126
Appendicitis, acute, 311
Arthritis, rheumatoid, antibiotic treatment questionable, 422; rheumatoid, skin rash following gold therapy, 423
Aspergillosis of lungs, 447
Asthma, surgical treatment, dorsal sympathetic ganglionectomy, 219

BACITRACIN, treatment of impetigo, 318
Bladder, cancer, results of treatment, 459; prostatic obstruction of bladder neck, 222
Blastomycosis of lungs, 449
Blood, dyscrasias, *see also* Anemia; dyscrasias, diagnosis of hemophilia in newborn, 501; dyscrasias, leukopenia due to sulfonamides, 422
Blood pressure, high, due to pheochromocytoma, 408; high, essential hypertension, clinical and pathologic characteristics, 48; high, essential hypertension, treatment, 136; low, orthostatic hypotension and orthostatic tachycardia, 475
Brain, hemorrhage in essential hypertension, (facing pages) 48, 136; surgery, transorbital lobotomy in treatment of schizophrenia, 392
Breast cancer, treatment with estrogens and x-rays, 429; lesions, differential diagnosis, 34
Breech presentation, analysis of 435 deliveries, 137
Bromides, in treatment of epilepsy, 456
Bronchi, bronchostenosis of inflammatory, probably nonspecific origin, 274; cancer, 300
Brown, John, novelist-physician, 505
Burns, total reconstruction of features after facial burns, 187

CALCIFEROL, treatment of lupus vulgaris, 422
Cancer, intrathoracic extrapulmonary, 6; of bladder, results of treatment, 459; of breast, differential diagnosis, 34; of breast, treatment with x-ray and estrogens, 429; of larynx, 379; of lip, 356; of lungs, 300; of mouth, medical and dental aspects, 355; of pancreas, with pulmonary and spinal metastases, 469; of rectum and colon, 120; of stomach, diagnosis, course, and prognosis, 201; of thyroid, treated with radioactive iodine, 386; present status of therapy, 89; x-ray and estrogen treatment of advanced disease, 429
Celiac disease, differential diagnosis, 501
Central nervous system, multiple sclerosis, diagnosis and treatment, 127; multiple sclerosis, physical therapy recommended, 228; syphilis, treated with penicillin and malaria, 28
Cesarean section, in breech delivery, 140
Cheyne-Stokes, respiration, in apparently normal patient, 256
Children, enuresis in, 502
Cholecystitis, *see* Gallbladder
Cholecystostomy, in treatment of acute cholecystitis, 365
Climacteric, male, impotency in, 330
Coccidioidomycosis of lungs, 449
Colic, renal, 314; renal, treatment, 407
Colon and rectum, lesions of, 120
Conjunctivitis, penicillin treatment, 329
Convulsive disorders in adults, 452
Coronary arteries, occlusion, 315; occlusion, mistaken electrocardiographic diagnosis, 66; syphilitic stenosis of ostia, 372; thrombosis, heparin and dicumarol for cardiac infarction, 330
Cripples, international cooperation in orthopedics, 250
Croup, spasmodic, treatment with aminophyllin suppositories, 180

DEMODEX folliculorum, as cause of rosacea, 480
Dentist, role in diagnosis of oral cancer, 355
Desoxycorticosterone, treatment of Addison's disease, 329
Diabetes mellitus, treatment of acidosis, 83
Diarrhea, clinical management, 1; infantile, treatment with oral streptomycin, 329
Dicumarol and heparin, for cardiac infarction, 330
Diet, low carbohydrate, in tuberculosis, 255; rice, in treatment of essential hypertension, 136
Dilantin, in treatment of epilepsy, 457
Diuretics, mercurial, oral administration, 179
Diverticulitis, of rectum and colon, 120
Duodenum, ulcer of, surgical aspects, 229
Dysentery, amebic, *see* Amebiasis

EAR, inner, streptomycin damage to vestibular apparatus, 160
Eclampsia, prophylaxis and treatment, 107
Electrocardiography, errors in diagnosis, 66
Electrocardiography, experiments advance interpretation, 378
Electrolyte, metabolism disturbances in nephrotic syndrome, 281
Endocarditis, bacterial, in elderly patients, 433; subacute bacterial, antibiotic therapy, 145; subacute bacterial, penicillin injections vs. continuous drip, 179
Enuresis in children, 502
Epilepsy in adults, 452
Epinephrine, production by pheochromocytoma, 408
Estrogens, synthetic, treatment of breast cancer, 429

FACE, total reconstruction following burns, 187
Floraquin, treatment of trichomoniasis, 502
Focal infection, nervous, functional and asthenic manifestations, 438
Folic acid, in treatment of anemia and sprue, 98
Food poisoning, as cause of diarrhea, 3

Foot, painful conditions of foot and ankle, 292
Foreign bodies, coin in stomach, 423
Fowler's solution in treatment of chronic myeloid leukemia, 83
Fungus disease of lungs, 443

GALLBLADDER inflammation, acute, 312; inflammation, cholecystostomy in treatment of acute cholecystitis, 365
Gamma globulin, effect on later stages of measles, 180
Gastric, *see* Stomach
Geriatrics, bacterial endocarditis in the elderly, 433
Glutamic acid in treatment of epilepsy, 457
Goiter, exophthalmic, *see* Graves' disease; treatment with radioactive iodine, 383
Gold therapy for arthritis, skin rash due to, 423
Graves' disease and neurocirculatory asthenia, differential diagnosis, 83
Guterman test for pregnancy, 179

HEALTH, definition, 95
Heart arrhythmia, orthostatic tachycardia and orthostatic hypotension, 475; block, treatment, 316; coronary occlusion, 315; failure, congestive, treatment, 483; disease, antibiotic therapy of subacute bacterial endocarditis, 145; disease, bacterial endocarditis in elderly, 433; disease, errors in electrocardiographic diagnosis, 66; disease, penicillin in subacute bacterial endocarditis, 179; disease, syphilitic stenosis of coronary ostia, 373; electrocardiography, errors in diagnosis, 66; electrocardiography, experiments advance interpretation, 378; infarction, treatment with heparin and dicumarol, 330; surgery of, 132
Hemophilia, diagnosis in newborn, 501
Heparin and dicumarol for cardiac infarction, 330
Hepatitis, acute viral, treatment, 255
Hormones, gonadotrophic, in treatment of incompletely descended testes, 422; interrelation in normal menstruation (chart), facing page 419; in treatment of breast cancer, 430; in treatment of cancer, 90
Hypertension, *see* Blood pressure, high
Hypogonadism, causes and treatment, 42
Hypotension, orthostatic, and orthostatic tachycardia, 475

ILEOSTOMY, care of, 126
Impetigo, treatment, 318
Impotency in male climacteric, 330
Infantile paralysis, *see* Poliomyelitis
Infants, diarrhea in, 4
Infection, focal, chronic, nervous, functional, and asthenic manifestations, 438
International cooperation in relation to welfare of cripples, 250
Intervertebral disk, ruptured, 423
Intestines, disease, rectal diagnosis, 388; infection with schistosoma mansoni, 330
Iodides, treatment of pulmonary mycosis, 443
Iodine, radioactive, in treatment of exophthalmic goiter, 263; radioactive, in treatment of thyroid disease, 383
Iron, intravenous administration in anemia, 330
Isotopes in treatment of cancer, 92; treatment of exophthalmic goiter with radioiodine, 263; radioactive iodine for treatment of thyroid disease, 383

JOINTS, cracking sound in, 423

KIDNEYS, colic, 314; lithiasis, management of, 212; nephrotic syndrome and disturbances in electrolyte metabolism, 281; normal and diseased (color photographs), facing page 218; treatment of renal colic, 407

LABOR, conduct of, analysis of 435 breech deliveries, 137
Larynx, cancer, 379
Leukemia, chronic myeloid, treatment with Fowler's solution and/or urethane, 83
Leukopenia, due to sulfonamides, 422
Lever, Charles, novelist-physician, 506
Lip cancer, 356
Lithiasis, renal, management of, 212
Liver inflammation, treatment of acute viral hepatitis, 255
Lobotomy, transorbital, in treatment of schizophrenia, 392
Lungs, bronchostenosis of inflammatory, probably nonspecific origin, 274; cancer, metastatic, from pancreas, 469; fungus disease, 443; surgical diseases, 299
Lupus vulgaris, treatment with calciferol, 422

MALARIA, therapeutic, used with penicillin for central nervous system syphilis, 28
Malignant disease, *see* Cancer
Maternal mortality at record low, 112
Measles, effect of gamma globulin after early stage, 180
Mebaral in treatment of epilepsy, 457
Mediastinum, tumors, diagnosis and surgical treatment, 6
Medicine in Portugal, 496
Meningitis, management of cases with meningeal signs, 481
Menstruation, normal, physiology (chart), facing page 418
Mental patients, thyroid function in, 273
Mercurial diuretics, oral administration, 179
Mesantoin in treatment of epilepsy, 457
Miscarriage, *see* Abortion
Moniliasis of lungs, 443
Mouth, cancer, medical and dental aspects, 355
Multiple sclerosis, diagnosis and treatment, 127; physical therapy recommended, 228
Mycosis of lungs, 443

NEUROCIRCULATORY asthenia and Graves' disease, differential diagnosis, 83
Nephrotic syndrome and disturbances in electrolyte metabolism, 281
Nitrogen mustard in treatment of cancer, 91
Nose drops, Tersavin, 68
Nutrition, recent progress in, 97

ORAL, *see* Mouth
Orbit, fracture-dislocation of zygoma and orbit, 400
Orthopedics, international cooperation in relation to welfare of cripples, 250
Ovaries, cystic condition not due to progesterone, 256

PANCREAS, cancer with pulmonary and spinal metastases, 469; inflammation, acute hemorrhagic, 314
Paredrine hydrobromide in treatment of orthostatic hypotension, 475
Parkinson's disease, surgical treatment, 83
Pellagra, treatment, 101
Penicillin, absorption by mouth, 83; injection vs. continuous drip in subacute bacterial endocarditis, 179; in prevention of recurrent rheumatic fever, 400; reaction to procaine penicillin, 501; treatment of conjunctivitis, 329; treatment of impetigo, 318; treatment of pneumonia in children, 256; treatment of sinusitis, not responsible for loss of smell and taste, 256; treatment of subacute bacterial endocarditis, 145; treatment of syphilis, 22
Peptic ulcer, perforated, 313; surgical aspects of duodenal ulcer, 229
Pernicious anemia, treatment with folic acid and vitamin B_{12}, 99; treatment with vitamin B_{12}, 306
Phenobarbital in treatment of epilepsy, 457
Pheochromocytoma, diagnosis and treatment, 408
Physical therapy in treatment of multiple sclerosis, 228; in treatment of poliomyelitis, 49
Physicians, the doctor as novelist, 503
Pituitary failure as cause of testicular dysfunction, 45; tumor as cause of hypogonadism, 45
Plastic surgery, total facial reconstruction following burns, 187
Pneumonia in children, penicillin treatment, 256
Poliomyelitis treatment, 49
Polyposis of rectum and colon, 120
Portugal, medicine in, 496
Posture, effect on orthostatic hypotension and orthostatic tachycardia, 475

Pregnancy, complications, eclampsia, prophylaxis and treatment, 107; complications, hyperthyroidism, contraindications to use of propyl thiouracil, 502; complications, syphilis, 28; diagnosis, Guterman test for urinary pregnandiol, 179
Procaine, reaction to procaine penicillin, 501
Prostate enlargement and bladder neck obstruction, 222
Psychoneurosis as cause of diarrhea, 5

RABELAIS, Francois, novelist-physician, 503
Radioiodine in treatment of exophthalmic goiter, 263
Rectum and colon, lesions of, 120; examination in diagnosis of intestinal disease, 388; treatment of spastic rectal sphincter, 255
Refrigeration anesthesia for amputation for vascular disease, 492
Renal, *see* Kidneys
Respiration, Cheyne-Stokes, in apparently normal patient, 256
Rheumatic fever, treatment of acute phase, 398
Roentgen rays in treatment of cancer, need for improvement in practice, 92; treatment of advanced cancer, 429
Rosacea, treatment, 480

SCHISTOSOMA mansoni, infections of intestinal tract, 330
Schizophrenia, 169; treatment by transorbital lobotomy, 392
Sinusitis, penicillin treatment not responsible for loss of smell and taste, 256
Skin rash due to gold therapy for arthritis, 423; tuberculosis, calciferol treatment of lupus vulgaris, 422
Skull, fracture-dislocation of zygoma and orbit, 400
Smollett, Tobias, novelist-physician, 504
Sphincter, rectal, treatment of spasticity, 255
Spine, intervertebral disk, ruptured, 423
Sprue, treatment with folic acid and vitamin B_{12}, 98; treatment with vitamin B_{12}, 310
Steatorrhea, differential diagnosis of celiac disease and other causes, 501
Stilbestrol, ineffective in acne, 256; in prevention of chronic miscarriage, 82
Stomach, cancer, diagnosis, course, and prognosis, 201; coin in, 423; ulcer, perforated, 313
Stones in kidneys, 212
Streptomycin, damage to vestibular apparatus, 160; sensitivity, 83; treatment of subacute bacterial endocarditis, 145; treatment of impetigo with dihydrostreptomycin, 318; treatment of infantile diarrhea, 329
Sulfadiazine in prevention of recurrent rheumatic fever, 399; treatment of meningococcus meningitis, 482
Sulfonamide compounds in treatment of subacute bacterial endocarditis, 145; leukopenia due to, 422
Sympathectomy, dorso-lumbar, in treatment of essential hypertension, 136
Sympathetic ganglionectomy, dorsal, in treatment of intractable asthma, 219
Syphilis, penicillin treatment, 22; stenosis of coronary ostia, 372

TACHYCARDIA, orthostatic, and orthostatic hypotension, 475
Television as teaching aid in London hospital, 95
Tersavin, new nasal medication, 68
Testes, dysfunction, 42; undescended, treatment with gonadotrophic hormones, 422
Thiouracil, propyl, not contraindicated by auricular fibrillation, 329; propyl, risks of administration during pregnancy, 502; sensitivity, 422; propyl, in treatment of thyrotoxicosis, 255
Thyroid, disease treated with radioactive iodine, 387; hyperthyroidism, exophthalmic goiter treated with radioiodine, 263; hyperthyroidism of pregnancy, risks in use of propyl thiouracil, 502; function in mental patients, 273; thyrotoxicosis treated with propyl thiouracil, 255
Thoracic tumors, extrapulmonary, diagnosis and surgical treatment, 6
Toxemia of pregnancy, prophylaxis and treatment of eclampsia, 107
Trichomoniasis, treatment of vaginitis, 179, 502
Tridione in treatment of epilepsy, 457
Tuberculosis, low carbohydrate diet in, 255; of lungs and pulmonary metastases from pancreatic cancer, 469; of skin, calciferol treatment of lupus vulgaris, 422
Tumors of breast, differential diagnosis, 34

URETHANE, in treatment of cancer, 91; in treatment of chronic myeloid leukemia, 83
Urine, incontinence, enuresis in children, 502

VAGINITIS, treatment of trichomoniasis, 502; trichomonal, 179
Varicose veins, etiology, 234; surgical treatment, 113
Vascular disease, technic of amputation with refrigeration anesthesia, 492
Veins, varicose, surgical treatment, 113
Vertigo due to vestibular damage from streptomycin, 160
Vestibular apparatus, streptomycin damage, 160
Vitamins, B_{12} in treatment of megaloblastic anemias, 303; B_{12} in treatment of pernicious anemia and sprue, 100

WHOOPING cough, relative therapeutic value of vaccine, hyperimmune serum, and aureomycin, 423

X-RAYS, *see* Roentgen rays

ZYGOMA, fracture-dislocation of zygoma and orbit, 400

AUTHOR INDEX—VOLUME VI

Adair, Frank E., Treatment of advanced malignant disease: synthetic estrogens and x-ray therapy, 429
Andosca, John B., and Foley, John A., Fungus disease of the lungs, 443
Ayres, Samuel, Jr., Treatment of rosacea, 480
Bass, Rose D., *see* Becker, Marvin C.
Beck, Claude S., Surgery of the heart, 132
Becker, Marvin C., Bass, Rose D., and Robbins, Charles M., Pheochromocytoma: diagnosis and treatment, 408
Blades, Brian, Surgical treatment of asthma, 219
Brown, James Barrett, and Fryer, Minot P., Fracture-dislocation of the zygoma and orbit, 400
Burns, Edgar, Treatment of renal colic, 407
Caplan, Leslie, Schizophrenia, 170
Carlisle, J. M., *see* Schmatolla, E.
Carter, J. Bailey, *see* Traut, Eugene F.
Cattell, Richard B., Lesions of the colon and rectum: malignancies, polyposis and diverticulitis, 120
Clark, R. Lee, Jr., The present status of cancer therapy, 89
Crile, George, Jr., Radioactive iodine for treatment of thyroid disease, 383
Curtis, Arthur C., Modern treatment of syphilis, 22
Dennen, E. H., and Fisher, R. L., Analysis of 435 consecutive breech deliveries, 137
Eger, Sherman A., and Wagner, Frederick B., Jr., Etiology of varicose veins, 234
Finney, George G., Surgical aspects of duodenal ulcer, 229
Fisher, R. L., *see* Dennen, E. H.
Foley, John A., *see* Andosca, John B.
Fryer, Minot P., *see* Brown, James Barrett
Geschickter, Charles F., Differential diagnosis between malignant and benign breast lesions, 34
Gibson, A., *see* Schmatolla, E.
Gottlieb, A. M., Syphilitic stenosis of the coronary ostia diagnosed during life, 373
Graham, Evarts A., Surgical diseases of the lungs, 299
Gray, Howard K., and Lofgren, Karl A., Cholecystostomy in the treatment of acute cholecystitis, 365
Griffith, George C., *see* Yuskis, Anton S.
Guilbert, G. D., and Rothstein, Emil, Streptomycin damage to the vestibular apparatus; one to two year follow-up, 160
Gumbiner, Stanley H., *see* Traut, Eugene F.
Haines, Samuel F., *see* Kelsey, Mavis P.
Hansen, Jens L., *see* Kjaer, Tage
Harrington, Stuart W., Intrathoracic extrapulmonary tumors: diagnosis and surgical treatment, 6
Higgins, Charles C., Management of patients with renal lithiasis, 212
Holbrook, W. Paul, and van Ravenswaay, Arie C., Treatment of acute rheumatic fever, 398
Jackson, Chevalier L., Cancer of the larynx, 379
Jaenike, Richard, Treatment of alcoholism, 320
Jones, Charles H., Social adjustment following transorbital lobotomy, 392
Keating, F. Raymond, *see* Kelsey, Mavis P.
Kelsey, Mavis P., Haines, Samuel F., and Keating, F. Raymond, The treatment of exophthalmic goiter with radioiodine, 263
Kjaer, Tage, Hansen, Jens L., and Smidt, Carsten M., Bronchostenosis of inflammatory, probably nonspecific origin, 274
Kneeland, Yale, Jr., Management of cases with meningeal signs, 481
Kretschmer, Herman L., The treatment of bladder neck obstruction, 222
Leake, Chauncey D., The clinical management of diarrheas, 1
Lewin, Philip, Painful conditions of the foot and ankle, 292
Lofgren, Karl A., *see* Gray, Howard K.
Logue, Bruce, Treatment of heart block, 316
Maimon, Samuel N., and Palmer, Walter Lincoln, Gastric cancer; diagnosis, course, and prognosis, 201
Martland, Harrison S., Essential hypertension; clinical and pathologic characteristics, 48; Treatment of essential hypertension, 136
McCullagh, E. Perry, Testicular dysfunction, 42
McIndoe, Sir Archibald, Total facial reconstruction following burns, 187
McQuarrie, Irvine, and Ziegler, Mildred M., Disturbances in electrolyte metabolism of patients with nephrotic syndrome, 281
Medlar, Robert E., Surgical treatment of varicose veins, 113
Meller, Robert L., and Resch, Joseph A., Convulsive disorders in adults, 452
Mendes Ferreira, Antonio E., Medicine in Portugal, 496
Mengert, William F., Prophylaxis and treatment of eclampsia, 107
Meyerding, Henry W., International cooperation in world medicine; its relation to the welfare of cripples, 250
Miller, J. Lowry, Treatment of impetigo, 318
Minnich, William R., Treatment of congestive heart failure, 483
Moorman, Lewis J., and Morrison, J. W., Carcinoma of the pancreas, with metastasis in the lungs and spinal column, 469
Morrison, J. W., *see* Moorman, Lewis J.
National Foundation for Infantile Paralysis, Treatment of infantile paralysis, 49
Palmer, Douglass, Present day rectal diagnosis, 388
Palmer, Walter Lincoln, *see* Maimon, Samuel N.
Podolsky, Edward, The doctor as novelist, 503
Pratt, Gerald H., Amputation for vascular disease with refrigeration anesthesia, 492
Priest, Walter S., and Smith, Jacques, M., Antibiotic therapy of subacute bacterial endocarditis, 145
Reese, Hans H. F., Diagnosis and treatment of multiple sclerosis, 127
Resch, Joseph A., *see* Meller, Robert L.
Robbins, Charles M., *see* Becker, Marvin C.
Robinson, Hamilton B. G., Medical and dental aspects of oral malignancy, 355
Rock, John, *see* Sturgis, Somers H.
Rothstein, Emil, *see* Guilbert, G. D.
Ryan, Robert E., Tersavin; a new nasal medication, 68
Schmatolla, E., Gibson, A., and Carlisle, J. M., Crystalline vitamin B_{12} in the treatment of megaloblastic anemias, 303
Smidt, Carsten M., *see* Kjaer, Tage
Smith, Jacques M., *see* Priest, Walter S.
Solis-Cohen, Myer, Nervous, functional, and asthenic manifestations of focal infection, 438
Spies, Tom D., Recent progress in nutrition, 97
Stroud, William D., Errors in electrocardiographic diagnosis, 66
Sturgis, Somers H., and Rock, John, The physiology of normal menstruation, facing page 418
Thomas, Gilbert J., Cancer of the urinary bladder, 459
Thorek, Philip, The acute abdomen, 311
Traut, Eugene F., Carter, J. Bailey, Gumbiner, Stanley H., Bacterial endocarditis in the elderly, 433
van Ravenswaay, Arie C., *see* Holbrook, W. Paul
Wagner, Frederick B., Jr., *see* Eger, Sherman A.
Yuskis, Anton S., and Griffith, George C., Orthostatic hypotension and orthostatic tachycardia, 475
Ziegler, Mildred M., *see* McQuarrie, Irvine

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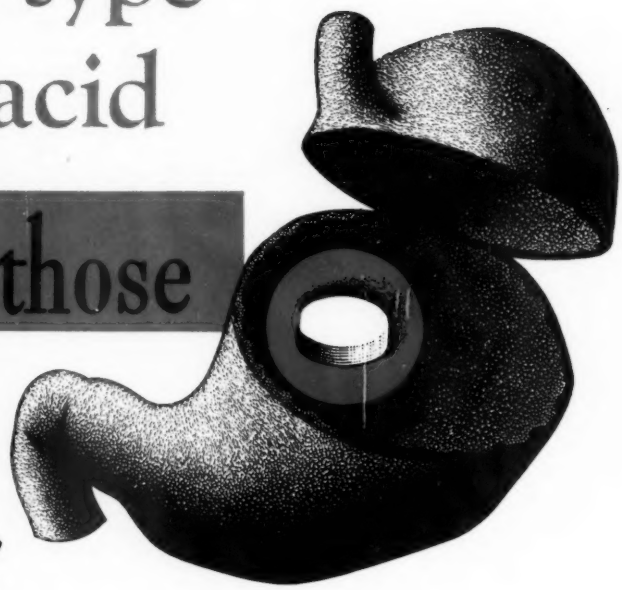

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